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Note

Microwave-assisted efficient preparation of novel carbohydrate tetrazole derivatives

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Abstract—A series of novel N-1, N-2 and S-5 saccharide substituted tetrazole derivatives linked at anomeric and nonanomeric positions were obtained from commercial tetrazoles under microwave irradiation. Yields are compared with conventional methodologies.

Keywords: Tetrazoles; Glycosyl tetrazoles; Microwave irradiation

A number of tetrazole derivatives exhibit biological activities and have found applications as carboxylic surrogates.[1] The development of tetrazole chemistry during the past 20 years can be ascribed to their diverse applications in medicine, biochemistry, agriculture, photography, information recording systems, explosives and others.[2,3] The ability of tetrazole compounds to mimic the carboxylic functionality has motivated the incorporation of tetrazole derivatives into biologically active molecules. This has led to applications in therapy resulting in compounds with anti-hypertensive, anti-allergic and antibiotic activities.[4]

Various modifications of the structure of tetrazoles have been carried out in order to obtain compounds with different physicochemical properties and subsequently with different pharmacodynamic and pharmacokinetic properties.[5] Novel methods of synthesis of substituted tetrazoles have been developed in recent years, including a simple and effective alkylation method for the synthesis of mono- and di-substituted tetrazoles with various frameworks. It has been postulated that regardless of the nature of the alkylating agent and the properties of the reaction medium, the alkylation of tetrazole and 5-substituted tetrazoles results in the formation of the corresponding 1- and 2-substituted tetrazoles. This reaction has great theoretical interest, since it may serve as a convenient model for the study of heterocyclic substrates with dual reactivity. Various groups can be used as alkylating agents, including sulfuric and aromatic sulfonic acid esters, in addition to simple alkyl halides.[3] Little attention, however, has been paid to carbohydrate analogues.

The application of microwave irradiation to organic synthesis for conducting reactions at accelerated rates is an emerging technique. In fact, in recent years, the use of microwaves has become popular among chemists both as a means to improve classical organic reactions (shortening reaction times and/or improving yields) and promote new reactions.[6] Availability of suitable commercial microwave equipments, domestic ovens and monomode reactors has also contributed to the development of this technique significantly.[7]

Knowing the broad spectrum of biological activities and the significant applications of the tetrazole ring

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systems, we have focussed our interest on improving the synthesis of saccharide tetrazole derivatives. The purpose of our research was an attempt to simplify tetrazole substitution by considering different heating modes (microwave irradiation and oil bath) and to prepare a number of carbohydrate heterocyclic derivatives of potential synthetic and pharmacological interest. To date, we are not aware of any report concerning the preparation of 1- and 2-substituted carbohydrate tetrazole derivatives involving the use of microwaves as the heating source. In the method reported therein, saccharide substitution of tetrazoles was accomplished using a domestic microwave oven specially modified for organic synthesis and an open vessel.

Thus, in the present study, novel saccharide substituted tetrazoles were synthesized starting from 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**1**) or methyl 2,3,6-tri-*O*-benzyl-4-*O*-triflyl-α-D-glucopyranoside (**2**) in reaction with commercial tetrazoles (Scheme 1) under microwave irradiation. The reactions were carried out by mixing the electrophilic agent **1** or **2**, potassium carbonate, and the respective commercial tetrazole compound in acetone (Scheme 1). After the appropriate time (Table 1), complete conversion to the corresponding product was monitored by TLC. To check the possible specific effect of microwaves, results obtained in a microwave oven were compared with conventional heating (Δ) in the same conditions.

Although conversions were obtained through both conditions, the isolated yields were improved and the reaction time was shortened in the case of the microwave reaction conditions. The compounds obtained in this work are novel, with the exception of **6e**.[8]

^{1}H and ^{13}C NMR analysis of the respective products clearly confirmed the site of substitution of the corresponding tetrazoles. ^{13}C NMR spectroscopy is particularly useful in this respect. The literature shows that the ^{13}C NMR shifts for C-5 (C-tetrazolic) for the 2-substituted isomer is consistently 10 ppm at higher field as compared to that for the corresponding 1-substituted isomer.[9,10] It is interesting to point the unequivocal characterization of the isomeric tetrazoles **6a** and **6b**, **6c** and **6d**, **7b** and **7c**. HMBC experiments were carried out for structure confirmation and revealed that the cross correlation of H-1′ and H-4′ with the tetrazolic carbon atoms occurs solely in derivatives **6a**, **6c** and **7b**, respectively, due to the ^{3}J coupling.

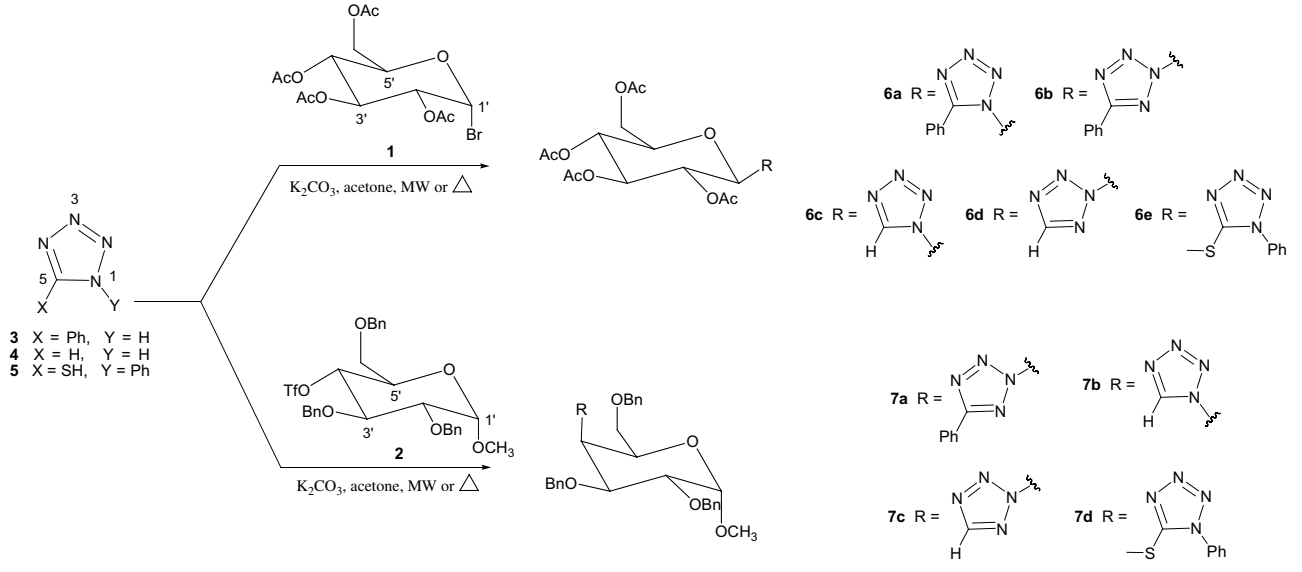
Table 1. Comparative glycosylation of tetrazoles under microwave irradiation and under classical conditions

Tetrazole	Product	Microwave irradiation		Classical reactions	
		Time (h)	Yield (%)	Time (h)	Yield (%)
3	**6a**	2.75	10	18.0	8
3	**6b**	2.75	64	18.0	56
4	**6c**	2.0	37	8.0	27
4	**6d**	2.0	41	8.0	27
5	**6e**	0.5	90	2.5	81
3	**7a**	1.30	84	48.0	84
4	**7b**	1.25	42	8.0	41
4	**7c**	1.25	30	8.0	25
5	**7d**	0.66	91	6.0	90

1. Experimental

1.1. General methods

Commercial reagents were used as received. Tetrazole derivatives **3**–**5** were obtained from Sigma–Aldrich. Dry acetone was prepared after agitation with potas-



Scheme 1.

sium carbonate for 24 h at room temperature, and then distilled. ^{1}H and ^{13}C NMR spectra were recorded using a BRUKER AVANCE DRX/ 200 or 400 apparatus in $CDCl_3$ with TMS as an internal standard. IR spectra were recorded on a Mattson Instruments Galaxy 3000. Melting points were determined on a Mettler FP80HT apparatus and are uncorrected. Elemental analyses were carried out using a Fisons EA1108 CHNS-O apparatus. The experiments were performed using a commercial microwave oven (Panasonic Junior Smart NNS53BH) specially modified for organic synthesis. The oven top was cut to accommodate a reflux condenser and a steel ring was used to avoid microwave leakage. The turnable dish was turned off.

1.2. Tetrazoles substitution by microwave irradiation

A mixture of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide[11] (**1**) or methyl 2,3,6-tri-*O*-benzyl-4-*O*-triflyl-α-D-glucopyranoside[12] (**2**) (1.0 mmol), tetrazole derivatives **3**, **4** or **5** (1.5 mmol), K_2CO_3 (15.0 mmol) and dried acetone (5 mL), was irradiated with microwaves for an appropriate length of time (Table 1). After complete conversion to the corresponding product as indicated by TLC, the solvent was removed under diminished pressure. The residue was diluted with CH_2Cl_2 and washed with water. The organic phase was dried over anhyd Na_2SO_4, filtered and the product was purified by silica gel chromatography (9.9:0.1–8.5:1.5 hexane–EtOAc) to afford the respective substituted tetrazoles.

1.3. Tetrazoles substitution by the conventional procedure

To a stirred soln of tetrazole **3**, **4** or **5** (1.5 mmol) and anhyd K_2CO_3 (15.0 mmol) in dry acetone (5 mL), **1**, or **2** (1.0 mmol) was added. The soln was stirred under reflux for an appropriate length of time (Table 1). After complete conversion to the corresponding product as indicated by TLC, the solvent was evaporated under diminished pressure. The residue was diluted with CH_2Cl_2 and washed with water (3×20 mL). The organic phase was dried over anhyd Na_2SO_4, filtered and the product was purified by silica gel chromatography (9.9:0.1–8.5:1.5 hexane–EtOAc) to give the respective substituted tetrazole.

1.4. 1-(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-glucopyranosyl)-5-phenyltetrazole (6a)

Colourless oil; $[\alpha]_D^{20}$ −43.8 (*c* 1.15, $CHCl_3$); IR (compression cell) *ν* 2924, 2852, 1744, 1366, 1206, 1033, 911, 731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.80 (d, 2H, $J_{o,m}$ 7.4 Hz, PhH_{ortho}), 7.67 (t, 1H, $J_{m,p}$ 7.4 Hz, PhH_{para}), 7.60 (t, 2H, PhH_{meta}), 5.92 (t, 1H, $J_{2',3'}$ 9.4 Hz, H-2′), 5.69 (d, 1H, $J_{1',2'}$ 9.4 Hz, H-1′), 5.33 (t, 1H, $J_{3',4'}$ 9.4 Hz, H-3′), 5.24 (t, 1H, $J_{4',5'}$ 9.4 Hz, H-4′), 4.29 (dd, 2H, $J_{6'a,6'b}$ 12.5, $J_{6'a,5'}$ 5.4 Hz, H-6′a), 4.24–4.21 (m, 1H, H-6′b), 4.01–3.98 (m, 1H, H-5′), 2.13, 2.06, 2.02, 1.83 (4s, 12H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): *δ* 170.50, 170.35, 169.32, 168.33 (C=O), 155.99 (C-5), 123.33 (C_{ipso}), 132.26, 129.58, 129.38 ($C_{arom.}$), 83.23 (C-1′), 75.23 (C-5′), 73.21 (C-3′), 69.60 (C-2′), 67.67 (C-4′), 61.98 (C-6′), 20.57, 20.39, 20.08 (*C*H_3CO). Anal. Calcd for $C_{21}H_{24}N_4O_9$: C, 52.94; H, 5.04; N, 11.76. Found: C, 52.94; H, 5.01; N, 10.83.

1.5. 2-(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-glucopyranosyl)-5-phenyltetrazole (6b)

White solid, mp 160–162 °C; $[\alpha]_D^{20}$ −3.6 (*c* 1.0, $CHCl_3$); IR (compression cell) *ν* 2924, 1749, 1370, 1212, 1035, 933, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.18–8.15 (m, 2H, Ph*H*), 7.51–7.48 (m, 3H, Ph*H*), 6.14 (d, 1H, $J_{1',2'}$ 9.4 Hz, H-1′), 5.97 (t, 1H, $J_{2',3'}$ 9.4 Hz, H-2′), 5.44 (t, 1H, $J_{3',4'}$ 9.4 Hz, H-3′), 5.34 (t, 1H, $J_{4',5'}$ 9.4 Hz, H-4′), 4.31 (dd, 1H, $J_{6'a,6'b}$ 12.6, $J_{6'a,5'}$ 5.0 Hz, H-6′a), 4.19 (dd, 1H, $J_{6'a,5'}$ 2.2 Hz, H-6′b), 4.06 (ddd, 1H, H-5′), 2.08, 2.05, 1.84 (3s, 12H, CH_3CO); ^{13}C NMR (50 MHz, $CDCl_3$): *δ* 170.58, 170.18, 169.39, 168.23 (C=O), 165.78 (C-5), 130.86, 128.97, 127.18 ($C_{arom.}$), 126.66 (C_{ipso}), 86.76 (C-1′), 75.17 (C-5′), 73.14 (C-3′), 69.85 (C-2′), 67.51 (C-4′), 61.52 (C-6′), 20.68, 20.55, 20.20 (CH_3CO). Anal. Calcd for $C_{21}H_{24}N_4O_9$: C, 52.94; H, 5.04; N, 11.76. Found: C, 53.49; H, 4.98; N, 11.95.

1.6. 1-(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-glucopyranosyl)-tetrazole (6c)

White solid, mp 165–167 °C; $[\alpha]_D^{20}$ −12.5 (*c* 1.0, $CHCl_3$); IR (compression cell) *ν* 2951, 1746, 1370, 1206, 1034, 922 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): *δ* 8.90 (s, 1H, H-5), 7.62 (d, 1H, $J_{1',2'}$ 9.3 Hz, H-1′), 5.98 (t, 1H, $J_{2',3'}$ 9.3 Hz, H-2′), 5.46 (t, 1H, $J_{3',4'}$ 9.3 Hz, H-3′), 5.34 (t, 1H, $J_{4',5'}$ 9.3 Hz, H-4′), 4.15–4.07 (m, 1H, H-5′), 4.33 (dd, 1H, $J_{6'a,6'b}$ 12.6, $J_{6'a,5'}$ 4.85 Hz, H-6′a), 4.26–4.22 (m, 1H, H-6′b), 2.18, 2.08 (2s, 12H, CH_3CO); ^{13}C NMR (50 MHz, $CDCl_3$): *δ* 170.61, 170.04, 169.45, 169.12 (C=O), 141.68 (C-5), 84.47 (C-1′), 75.62 (C-5′), 72.41 (C-3′), 70.42 (C-2′), 67.61 (C-4′), 61.49 (C-6′), 20.78, 20.64, 20.24, 19.29 (CH_3CO). Anal. Calcd for $C_{15}H_{20}N_4O_9$: C, 45.00; H, 5.00; N, 14.00. Found: C, 45.58; H, 4.99; N, 13.69.

1.7. 2-(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-glucopyranosyl)-tetrazole (6d)

White solid, mp 162–163 °C; $[\alpha]_D^{20}$ −5.4 (*c* 1.15, $CHCl_3$); IR (compression cell) *ν* 2951, 2924, 1744, 1369, 1208, 1033, 924 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): *δ* 8.62 (s, 1H, H-5), 6.17 (d, 1H, $J_{1',2'}$ 9.3 Hz, H-1′), 5.88 (t, 1H, $J_{2',3'}$ Hz, H-2′), 5.44 (t, 1H, $J_{3',4'}$ 9.3 Hz, H-3′), 5.32 (t, 1H, $J_{4',5'}$ 9.3 Hz, H-4′), 4.09–4.06 (m, 1H, H-

5′), 4.31 (dd, 1H, $J_{6'a,6'b}$ 12.60, $J_{6'a,5'}$ 4.8 Hz, H-6′a), 4.17 (d, 1H, H-6′b), 2.08, 2.04 (2s, 12H, CH_3CO); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.67, 170.30, 169.38, 168.52 (C═O), 153.68 (C-5), 86.84 (C-1′), 75.35 (C-5′), 73.11 (C-3′), 69.99 (C-2′), 67.57 (C-4′), 61.59 (C-6′), 20.82, 20.69, 20.28 (CH_3CO). Anal. Calcd for $C_{15}H_{20}N_4O_9$: C, 45.00; H, 5.00; N, 14.00. Found: C, 45.53; H, 5.01; N, 13.81.

1.8. 5-*S*-(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1-phenyl-5-thiotetrazole (6e)

Colourless oil, $[\alpha]_D^{20}$ −12.6 (*c* 1.05, $CHCl_3$); lit.[9] −13.0 (*c* 2.3, $CHCl_3$); IR (compression cell) *v* 2923, 1743, 1499, 1366, 1209, 1032, 911, 763, 689 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.56–7.51 (sl, 5H, Ph*H*), 5.78 (d, 1H, $J_{1',2'}$ 10.1 Hz, H-1′), 5.39–5.09 (m, 3H, H-2′, H-3′, H-4′), 4.28 (dd, 1H, $J_{6'a,6'b}$ 12.5, $J_{6'a,5'}$ 4.8 Hz, H-6′a), 4.17–4.06 (m, 1H, H-6′b), 3.91 (ddd, 1H, $J_{5',6'b}$ 9.8, $J_{5',4'}$ 2.1 Hz, H-5′), 2.04 (br s, 12H, 4CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.71, 170.05, 169.74, 169.59 (4C═O), 133.35 (C_{ipso}), 130.71, 130.11, 124.25 ($C_{arom.}$), 83.87 (C-1′), 76.61 (C-5′), 73.74 (C-3′), 69.91 (C-2′), 67.91 (C-4′), 61.62 (C-6′), 20.84, 20.71 (CH_3CO).

1.9. 2-(Methyl 2′,3′,6′-tri-*O*-benzyl-4′-deoxy-α-D-galactopyranos-4′-yl)-5-phenyltetrazole (7a)

Colourless oil; $[\alpha]_D^{20}$ +53.0 (*c* 1.70, $CHCl_3$); IR (NaCl) *v* 3100, 2950, 1540, 1510, 1460, 1210, 910, 740, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14–7.46 (m, 4H, Ph*H*), 7.35–7.21 (m, 4H, Ph*H*), 5.65 (dd, 1H, *J* 5.4, *J* 2.5 Hz, H-4′), 4.83 (d, 1H, $J_{1,2}$ 3.8 Hz, H-1′), 4.83 (d, 1H, *J* 11.9 Hz, CH_2Ph), 4.75 (d, 1H, *J* 11.6 Hz, CH_2Ph), 4.65 (d, 1H, *J* 11.9 Hz, CH_2Ph), 4.64 (d, 1H, *J* 11.6 Hz, CH_2Ph), 4.62 (dd, 1H, $J_{2',3'}$ 9.6 Hz, H-2′), 4.38–4.27 (m, 4H, H-3′, H-5′, 2CH_2Ph), 3.43 (s, 3H, OCH_3), 3.32 (dd, 1H, $J_{6'a,6'b}$ 9.6, $J_{6'a,5'}$ 5.6 Hz, H-6′a), 2.98 (dd, 1H, $J_{6'b-5}$ 7.5 Hz, H-6′b); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.84 (C-5), 138.38, 137.63, 137.48 (C_{ipso}), 130.38, 128.91, 128.54, 128.27, 127.98, 127.67, 127.17 ($C_{arom.}$), 99.47 (C-1′), 74.94 (C-5′), 74.82 (C-2′), 74.03, 73.87, 72.50 (*C*H_2Ph), 68.39 (C-6′), 66.60 (C-3′), 63.24 (C-4′), 55.79 (O*C*H_3). Anal. Calcd for $C_{35}H_{36}N_4O_5$: C, 52.94; H, 5.04; N, 11.76. Found: C, 52.94; H, 5.01; N, 11.83.

1.10. 1-(Methyl 2′,3′,6′-tri-*O*-benzyl-4′-deoxy-α-D-galactopyranos-4′-yl)tetrazole (7b)

Colourless oil; $[\alpha]_D^{20}$ +26.5 (*c* 1.20, $CHCl_3$); IR (NaCl) *v* 2900, 1500, 1460, 1360, 1200, 1110, 740, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (s, 1H, H-5), 7.35–7.12 (m, 18H, Ph*H*), 5.22 (dd, 1H, $J_{4',5'}$ 5.0, $J_{4',3'}$ 2.0 Hz, H-4′), 4.79–4.18 (m, 6H, CH_2Ph), 4.78 (d, 1H, $J_{1',2'}$ 3.8 Hz, H-1′), 4.36–4.33 (m, 1H, H-5′), 4.21 (dd, 1H, $J_{3',4'}$ 4.7 Hz, H-3′), 3.92 (dd, 1H, $J_{2',3'}$ 10.0 Hz, H-2′), 3.44–3.38 (m, 1H, H-6′a), 3.41 (s, 3H, OCH_3), 2.85 (t, 1H, $J_{6'a,6'b} = J_{6'a,5'}$ 9.0 Hz, H-6′b); ^{13}C NMR (50 MHz, $CDCl_3$): δ 143.96 (C-5), 137.98, 137.58, 137.06 (C_{ipso}), 129.57, 128.70, 128.66, 128.25, 128.0, 127.91($C_{arom.}$), 99.15 (C-1′), 75.91 (C-2′), 74.90 (C-3′), 74.12, 73.79, 73.09 (*C*H_2Ph), 67.45 (C-6′), 65.76 (C-5′), 59.21 (C-4′), 56.03 (O*C*H_3). Anal. Calcd for $C_{29}H_{32}N_4O_5$: C, 67.44; H, 6.20; N, 10.85. Found: C, 67.64; H, 6.40; N, 10.83.

1.11. 2-(Methyl 2′,3′,6′-tri-*O*-benzyl-4′-deoxy-α-D-galactopyranos-4′-yl)tetrazole (7c)

Colourless oil; $[\alpha]_D^{20}$ +25.3 (*c* 2.15, $CHCl_3$); IR (NaCl) *v* 2900, 1500, 1460, 1360, 1290, 1210, 1100, 750, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (s, 1H, H-5), 7.30–7.21 (m, 15H, Ph*H*), 5.70 (dd, 1H, *J* 5.3, *J* 2.3 Hz, H-4′), 4.79–4.18 (m, 6H, CH_2Ph), 4.84 (d, 1H, $J_{1',2'}$ 3.8 Hz, H-1′), 4.46 (dd, 1H, $J_{2',3'}$ 10.0 Hz, H-2′), 4.38–4.25 (m, 2H, H-3′, H-5′), 3.41 (s, 3H, OCH_3), 3.29 (dd, 1H, $J_{6'a,6'b}$ 9.4, $J_{6'a,5'}$ 5.6 Hz, H-6′a), 2.85 (t, 1H, $J_{6'b,5'}$ 7.8 Hz, H-6′b); ^{13}C NMR (50 MHz, $CDCl_3$): δ 152.80 (C-5), 138.41, 137.57, 137.41 (C_{ipso}), 128.57, 128.54, 128.05, 128.0, 127.96 ($C_{arom.}$), 99.35 (C-1′), 75.65 (C-2′), 74.82 (C-5′), 74.16, 73.91, 72.61 (*C*H_2Ph), 68.22 (C-6′), 66.47 (C-3′), 63.14 (C-4′), 55.87 (O*C*H_3). Anal. Calcd for $C_{29}H_{32}N_4O_5$: C, 67.44; H, 6.20; N, 10.85. Found: C, 66.94; H, 6.43; N, 10.79.

1.12. 5-*S*-(Methyl 2′,3′,6′-tri-*O*-benzyl-4′-deoxy-α-D-galactopyranos-4′-yl)1-phenyl-5-thiotetrazole (7d)

Colourless oil; $[\alpha]_D^{20}$ +55.4 (*c* 1.89, $CHCl_3$); IR (NaCl) *v* 3100, 2800, 1600, 1500, 1460, 910, 750, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50–7.14 (m, 20H, Ph*H*), 5.11–5.10 (br s, 1H, H-4′), 4.78 (d, 1H, *J* 12.0 Hz, CH_2Ph), 4.65 (d, 1H, *J* 10.9 Hz, CH_2Ph), 4.60–4.54 (m, 3H, CH_2Ph), 4.59 (d, 1H, $J_{1',2'}$ 3.8 Hz, H-1′), 4.47 (d, 1H, *J* 12.0 Hz, CH_2Ph), 4.38–4.40 (br t, 1H, H-5′), 4.20 (dd, 1H, $J_{3',2'}$ 9.8, $J_{3',4'}$ 4.1 Hz, H-3′), 3.77 (dd, 1H, $J_{6'a,6'b}$ 9.8, $J_{6'a,5}$ 5.5 Hz, H-6′a), 3.68 (dd, 1H, $J_{6'b,5}$ 6.5 Hz, H-6′b), 3.39 (s, 3H, OCH_3); ^{13}C NMR (50 Hz, $CDCl_3$): δ 154.22 (C-5), 138.19, 137.71, 137.57, 133.70 (C_{ipso}), 130.04, 129.55, 128.37, 128.29, 127.98, 127.77, 124.36 ($C_{arom.}$), 98.85 (C-1′), 77.15 (C-3′), 76.39 (C-2′), 73.67, 73.61, 72.77 (*C*H_2Ph), 70.24 (C-6′), 67.95 (C-5′), 55.51 (O*C*H_3), 54.45 (C-4′). Anal. Calcd for $C_{35}H_{36}N_4O_5S$: C, 67.30; H, 5.77; N, 8.97. Found: C, 66.94; H, 5.48; N, 9.36.

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