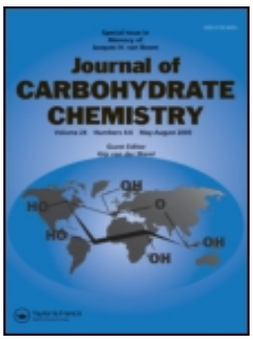

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Synthesis of Heteroanellated Pyranosides Starting from Methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-D-*erythro*-hexopyranosid-2-ylidenemalononitrile

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The hexopyranosid-2-ylidenemalononitrile **1** reacted with phenyl isothiocyanate in the presence of triethylamine to furnish (2*R*,4a*R*,6*S*,10b*S*)-8-amino-4a,6,10,10b-tetrahydro-6-methoxy-2-phenyl-10-phenylimino-4*H*-thiopyrano[3′,4′:4,5]py rano[3,2-*d*][1,3] dioxine-7-carbonitrile (**2**). Starting from **1**, cyclization with sulphur and diethylamine yielded (2*R*,4a*R*,6*S*,9b*R*)-8-amino-4,4a,6,9b-tetrahydro-6-methoxy-2-phenylthieno [2′,3′:4,5]pyrano[3,2-*d*][1,3]dioxine-7-carbonitrile (**3**), which could be transformed into the corresponding aminomethylenamino derivative **4** by treatment with triethyl orthoformate and ammonia. Intramolecular cyclization of **4** to yield (2*R*,4a*R*,6*S*,11b*R*)-4,4a,6,11b-tetrahydro-6-methoxy-2-phenyl[1,3]dioxino[4″,5″:5′,6′]pyrano[3′,4′:4,5]thieno [2,3-*d*]pyrimidin-7-amine (**5**) was achieved by using NaH as base. (2*R*,4a*R*,6*S*,9b*S*)-8-Amino-4a,6,9,9b-tetrahydro-6-methoxy-9-(4-methylphenyl-sulfonyl)-2-phenyl-4*H*-[1,3]-dioxino[4′,5′:5,6]pyrano[4,3-*b*]pyrrole-7-carbonitrile (**6**) was prepared by treatment of compound **1** with tosylazide and triethylamine.

Keywords Hexopyranosidylidenemalononitrile, Heteroanellated pyranosides, Anellated heterocycles, Nucleoside analogs

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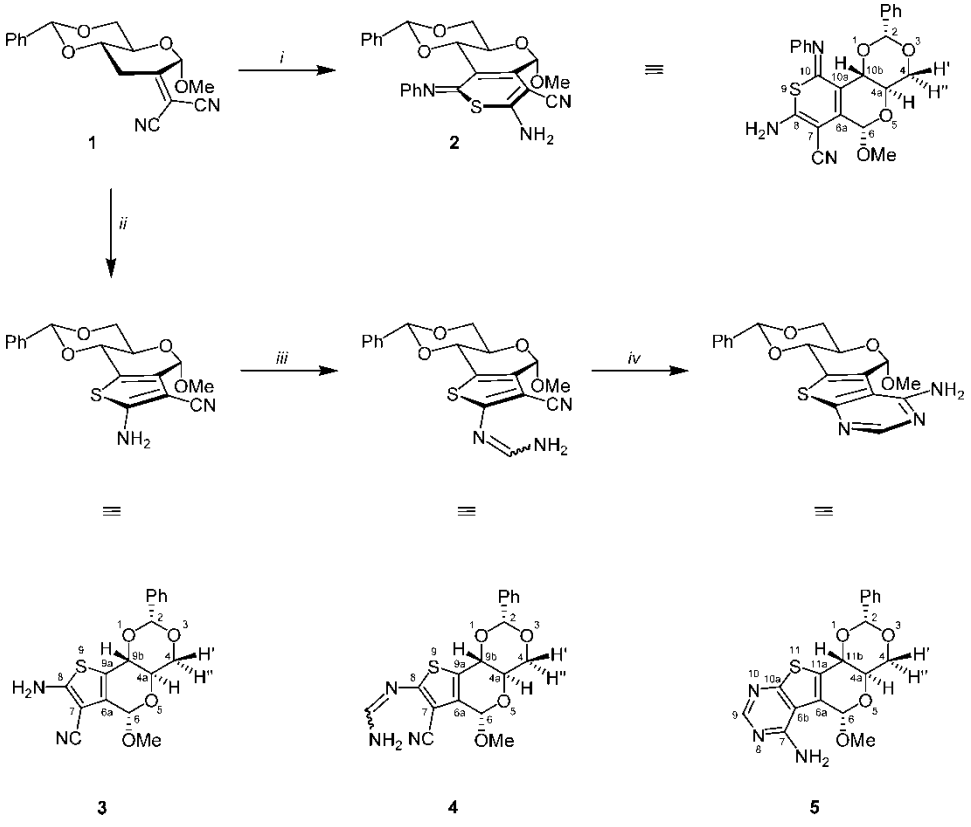
INTRODUCTION

The development of new methods for the synthesis of anellated monosaccharide derivatives has attracted a current interest in the organic synthesis because of the biologic importance that some compounds of this class have shown. The activities include main topics like remarkable anticancer,[1–3] enzyme inhibitory,[4–6] and anti-inflammatory effects[7] as well as actions as spruce budworm antifeedants[8] or as neuronal differentiation agents.[9] Continuing our studies about heterocyclic anellated monosaccharides,[10–14] herein we want to describe the synthesis of thieno and pyrrolo anellated pyranosides, respectively.

RESULTS AND DISCUSSION

The branched-chain pyranoside **1** can be synthesized in seven steps starting from D-glucose. The final reaction step of this synthetic sequence consisted of a Knoevenagel reaction of the corresponding hexopyranosid-2-ulose with malononitrile.[15] Caused by the strong electron-withdrawing effect of the neighboring dicyanomethylene group, the high CH acidity of H-3 in compound **1** could be used for the reaction with phenyl isothiocyanate in the presence of triethylamine at room temperature. After introductory attack of the carbanion arising from **1** at phenyl isothiocyanate, a nitrile cyclization occurred to furnish the (2*R*,4a*R*,6*S*,10b*S*)-8-amino-4a,6,10,10b-tetrahydro-6-methoxy-2-phenyl-10-phenylimino-4*H*-thiopyrano[3′,4′:4,5]pyrano[3,2-*d*][1,3]dioxine-7-carbonitrile (**2**) in 62% yield (Sch. 1). In the ^{13}C NMR spectrum the compound **2** showed in contrast to the starting material **1** only one nitrile group. The generated amino group appeared in ^{1}H NMR ($\delta = 5.27$) and also in IR ($\nu = 3439$, 3314, 3198 cm^{-1}). Due to the absence of a strong downfield shifted thioamide signal in ^{13}C NMR, the alternatively imaginable Dimroth rearrangement product could be excluded. These results are in concordance with the literature. Such reactions performed at room temperature preferably led to the formation of the thiopyran ring, while the corresponding dihydropyridinethiones were formed as a major product at higher temperatures.[16]

Recently, based on literature procedures,[17,18] we were able to synthesize thiophene *C*-nucleoside analogs by treatment of monosaccharide derivatives chain elongated through a 3,3-dicyanoprop-2-enyl group with elementary sulphur and triethylamine in DMF.[19] A comparably functionalization present in compound **1** should allow to prepare thieno anellated pyranoside. The reaction of **1** with sulphur and diethylamine in methanol instead of DMF as solvent afforded the (2*R*,4a*R*,6*S*,9b*R*)-8-amino-4,4a,6,9b-tetrahydro-6-methoxy-2-phenylthieno[2′,3′:4,5]pyrano[3,2-*d*][1,3]dioxine-7-carbonitrile (**3**) in 69% yield (Sch. 1). The successful anellation by this nitrile cyclization was proved mainly by the detectable new amino group in the ^{1}H NMR spectrum ($\delta = 6.57$) and in the IR spectrum ($\nu = 3356$, 3300, 3196 cm^{-1}).



Scheme 1: (*i*) PhNCS, Et_3N, DMF, 62%; (*ii*) S_8, Et_2NH, MeOH, 69%; (*iii*) $CH(OEt)_3$ 82%; (*iv*) NaH, DMF, 71%.

The α-aminonitrile structure element in the thiophene ring of **3** should allow a further cyclization. In contrast to earlier examinations,[19] the reaction of compound **3** with triethyl orthoformate/ammonia under reflux gave not directly the desired (2*R*,4a*R*,6*S*,11b*R*)-4,4a,6,11b-tetrahydro-6-methoxy-2-phenyl[1,3]dioxino[4″,5″:5′,6′]pyrano[3′,4′:4,5]thieno[2,3-*d*]pyrimidin-7-amine (**5**) but the open-chain (2*R*,4a*R*,6*S*,9b*R*)-8-(aminomethylenamino)-6-methoxy-4,4a,6,9b-tetrahydro-2-phenylthieno[2′,3′:4,5]pyrano[3,2-*d*][1,3]dioxine-7-carbonitrile (**4**). Nitrile cyclization could be achieved only after treating compound **4** with sodium hydride in DMF at room temperature, yielding **5** in 71% yield. In accordance with the structure, no signal for a nitrile group was visible in the ^{13}C NMR and in the IR spectrum of compound **5**. The amino group appeared in the ^1H NMR spectrum ($\delta = 6.88$) and in the IR spectrum ($\nu = 3486$ and $3284\,cm^{-1}$). Together with all other analytical data structure **5** was substantiated without any doubt also by the ^{13}C NMR shifts, which were determined using ^1H, ^{13}C correlation and COLOC experiments.

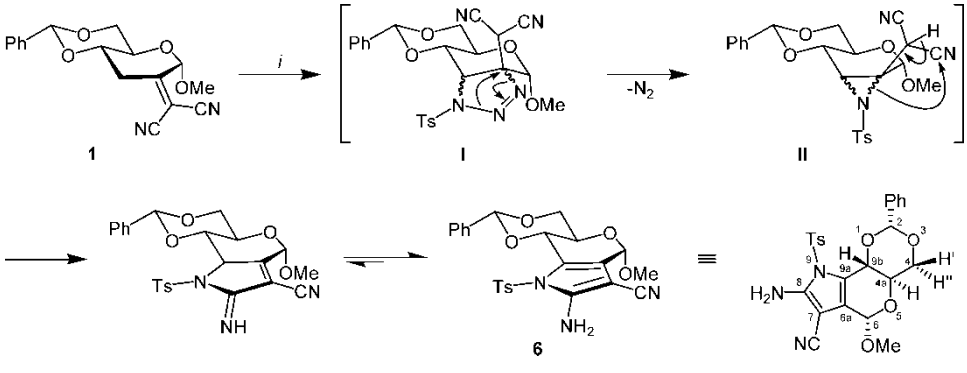
A further interesting, but not expected, anellation of compound **1** was observed in the reaction with tosylazide providing the (2*R*,4a*R*,6*S*,9b*S*)-8-amino-4a,6,9,9b-tetrahydro-6-methoxy-9-(4-methylphenylsulfonyl)-2-phenyl-4*H*-[1,3]dioxino[4′,5′:5,6]pyrano[4,3-*b*]pyrrole-7-carbonitrile (**6**) in 39% yield. Following the established reaction mechanism for the transformation of carbonyl compounds with tosyl azide as 1,3-dipolar cycloaddition,[20] we would like to postulate as first intermediate the triazoline **I** (Sch. 2). Then, nitrogen could split off to create the aziridine **II**, which undergoes a rearrangement to yield compound **6**. In conformity with the values of the elemental analysis, three nitrogen atoms were present in the molecule. The ^{1}H NMR, ^{13}C NMR, and IR data proved the existence of two phenyl rings only one cyano group, are an amine function.

In summary, hexopyranosid-2-ylidenemalononitrile **1** represents a suitable starting material to synthesize pyranosides fused with different types of heterocycles.

EXPERIMENTAL

General Methods

TLC was carried out on silica gel 60 GF_{254} (Merck, layer thickness 0.2 mm) with detection by UV light ($\lambda = 254$ nm) and/or by charring with 10% sulphuric acid in methanol. Silica gel 60 (0,063–0,200 mm) (Merck) was used for column chromatography with the solvent systems specified. Melting points were determined by using a Boetius melting point apparatus and are corrected. IR spectra were recorded with a Nicolet 205 FT-IR spectrometer. Specific rotations were determined with a Polar LμP (IBZ Messtechnik) or with a Gyromat HP (Dr. Kernchen GmbH). ^{1}H NMR (250.13 MHz and 300.13 MHz, respectively)



Scheme 2: (*i*) TsN_3, Et_3N, MeCN, 39%.

and ^{13}C NMR (62.9 MHz and 75.5 MHz, respectively) spectra were recorded on Bruker instruments AC 250 and ARX 300, with $CDCl_3$, [D_6]-DMSO or [D_6]-acetone as solvent. Calibration of spectra was carried out on solvent signals $CDCl_3$: δ (^1H) = 7.25, δ (^{13}C) = 77.0; [D_6]-DMSO: δ (^1H) = 2.50, δ (^{13}C) = 39.7; [D_6]-acetone: δ (^1H) = 2.04, δ (^{13}C) = 29.7. The ^1H and ^{13}C NMR signals were assigned by DEPT, two-dimensional ^1H, ^1H correlation, ^1H, ^{13}C correlation, and/or COLOC experiments. The mass spectra were recorded on an AMD 402/3 spectrometer (AMD Intectra GmbH). Elemental analysis were performed on a Leco CHNS-932 instrument. The solvents and liquid reagents were purified and dried according to recommended procedures.

(2*R*,4a*R*,6*S*,10b*S*)-8-Amino-4a,6,10,10b-tetrahydro-6-methoxy-2-phenyl-10-phenylimino-4*H*-thiopyrano[3′,4′:4,5]pyrano[3,2-*d*][1,3]dioxine-7-carbonitrile (2). A solution of **1** (312 mg, 1.0 mmol), phenyl isothiocyanate (0.12 mL, 1.0 mmol), and triethylamine (0.140 mL, 1.0 mmol) in anhydrous DMF (15 mL) was stirred for 5 h at rt. Then, the reaction mixture was poured into ice water (70 mL) and extracted with dichloromethane (3 × 20 mL). The combined extracts were washed with water (3 × 20 mL), dried (Na_2SO_4), and concentrated to leave a syrup. The raw product was chromatographed on a column of silica gel with 3:1 toluene/ethyl acetate to give, after recrystallization from diethyl ether/heptane, **2** (227 mg, 62%) as yellow crystals; mp > 200°C (decomposition); $[\alpha]_D^{22}$ +273° (*c* 1.0, $CHCl_3$); R_f 0.37 (toluene/ethyl acetate 4:1); IR (KBr): ν 3439, 3314, 3198 (NH_2), 2201 (CN), 1607, 1586 (C=C) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 3.60 (s, 3H, OMe), 3.93 (t, 1H, $J_{4',4''}$ 10.1 Hz, $J_{4',4a}$ 10.1 Hz, H-4′), 4.16–4.27 (m, 1H, H-4a), 4.39 (dd, 1H, $J_{4'',4a}$ 4.4 Hz, H-4″), 4.71 (d, 1H, $J_{10b,4a}$ 9.0 Hz, H-10b), 5.18 (s, 1H, H-6), 5.27 (s, 2H, NH_2), 5.72 (s, 1H, H-2), 6.80 (d, 2H, *o*-NPh), 7.15 (t, 1H, *p*-NPh), 7.26–7.51 (m, 7H, *m*-NPh, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.6 (OMe), 64.4 (C-4a), 69.0 (C-4), 74.7 (C-10b), 77.1 (C-7), 97.5 (C-6), 101.3 (C-2), 115.4 (CN), 118.8 (C-10a), 119.2, 124.8, 125.9, 128.0, 128.6, 129.7, 137.6 (Ph, NPh), 139.7 (C-6a), 146.9, 149.8, 160.3 (NPh, C-8, C-10); MS (EI, 70 eV): *m/z* (%) 447 (11) $[M]^+$, 149 (100).

Anal. Calcd for $C_{24}H_{21}N_3O_4S$: C, 64.41; H, 4.73; N, 9.38; S, 7.16. Found: C, 64.43; H, 4.67; N, 9.40; S, 6.94.

(2*R*,4a*R*,6*S*,9b*R*)-8-Amino-4,4a,6,9b-tetrahydro-6-methoxy-2-phenylthieno[2′,3′:4,5]pyrano[3,2-*d*][1,3]dioxine-7-carbonitrile (3). Diethylamine (0.11 mL, 1.1 mmol) was added to a suspension of **1** (312 mg, 1.0 mmol) and elementary sulphur (35 mg, 1.1 mmol) in anhydrous methanol (30 mL). The mixture was stirred for 2 h at 45°C, then filtrated and evaporated in vacuo. After purification by column chromatography (toluene/acetone 4:1) and recrystallization from dichloromethane/heptane, **3** (238 mg, 69%) was obtained as colorless needles; mp 207–209°C; $[\alpha]_D^{22}$ +18.6° (*c* 1.0, $CHCl_3$); R_f 0.39 (toluene/acetone 4:1); IR (KBr): ν 3356, 3300, 3196 (NH_2), 2226 (CN), 1518

(C═C) cm^{-1}; ^1H NMR (250 MHz, [D_6]-acetone): δ 3.53 (s, 3H, OMe), 3.91–4.09 (m, 2H, $J_{4',4a}$ 8.8 Hz, H-4′, H-4a), 4.29 (dd, 1H $J_{4',4''}$ 8.8 Hz, $J_{4'',4a}$ 3.4 Hz, H-4″), 4.72 (d, 1H, $J_{4a,9b}$ 8.2 Hz, H-9b), 5.33 (s, 1H, H-6), 5.80 (s, 1H, H-2), 6.57 (s, 2H, NH_2), 7.30–7.54 (m, 5H, Ph); ^{13}C NMR (63 MHz, [D_6]-acetone): δ 56.5 (OMe), 66.8 (C-4a), 69.5 (C-4), 76.0 (C-9b), 84.7 (C-7), 96.9 (C-6), 102.5 (C-2), 114.6 (CN), 120.5 (C-6a), 127.3, 128.9, 129.8, 133.7, (Ph), 138.7 (C-9a), 165.2 (C-8); MS (CI, isobutane): m/z (%) 345 (100) $[M+H]^+$.

Anal. Calcd for $C_{17}H_{16}N_2O_4S$: C, 59.29; H, 4.68; N, 8.13; S, 9.31. Found: C, 59.81; H, 4.74; N, 7.98; S, 9.07.

(2*R*,4a*R*,6*S*,9b*R*)-8-(Aminomethylenamino)-4,4a,6,9b-tetrahydro-6-methoxy-2-phenylthieno[2′,3′:4,5]pyrano[3,2-*d*][1,3]dioxine-7-carbonitrile (4). A solution of **3** (300 mg, 0.87 mmol) in triethyl orthoformate (10 mL) was heated for 2 h under reflux. Then the reaction mixture was concentrated under reduced pressure yielding a solid, which was dissolved in a saturated ethanolic solution of ammonia (15 mL) and stirred over night at rt. Evaporation in vacuo supplied a light yellow solid, which after treatment with charcoal in acetone was pure enough for the preparation of compound **5**. Column chromatography (toluene/acetone 2:1) furnished analytically pure **4** (305 mg, 82%) as colorless crystals; mp 262–265°C; $[\alpha]_D^{22}$ −80.5° (*c* 1.0, DMF); R_f 0.45 (toluene/acetone 2:1); IR (KBr): ν 3400, 3143 (NH_2), 2215 (CN), 1694 (C═C) cm^{-1}; ^1H NMR (250 MHz, [D_6]-DMSO): δ 3.46 (s, 3H, OMe), 3.81–4.03 (m, 2H, $J_{4',4a}$ 9.6 Hz, H-4′, H-4a), 4.27 (dd, 1H, $J_{4',4''}$ 9.5 Hz, $J_{4'',4a}$ 3.7 Hz, H-4″), 4.79 (d, 1H, $J_{4a,9b}$ 8.4 Hz, H-9b), 5.43 (s, 1H, H-6), 5.82 (s, 1H, H-2), 7.34–7.48 (m, 5H, Ph), 7.73 (s, 1H, N*H*H), 7.84 (t, 1H, C*H*NH_2), 8.10 (d, 1H, NH*H*); ^{13}C NMR (63 MHz, [D_6]-DMSO): δ 56.2 (OMe), 65.7 (C-4a), 68.2 (C-4), 74.4 (C-9b), 93.4 (C-7), 95.5 (C-6), 101.1 (C-2), 114.8 (CN), 124.4 (C-6a), 126.5, 128.3, 129.3, 132.7, (Ph), 137.4 (C-9a), 155.7 ($CHNH_2$), 168.2 (C-8); MS (70 eV): m/z (%) 371 (100) $[M]^+$.

Anal. Calcd for $C_{18}H_{17}N_3O_4S$: C, 58.21; H, 4.61; N, 11.31; S, 8.63. Found: C, 58.00; H, 4.69; N, 11.07; S, 8.35.

(2*R*,4a*R*,6*S*,11b*R*)-4,4a,6,11b-Tetrahydro-6-methoxy-2-phenyl-[1,3]dioxino[4″,5″:5′,6′]pyrano[3′,4′:4,5]thieno[2,3-*d*]pyrimidin-7-amine (5). A solution of **4** (300 mg, 0.81 mmol) in anhydrous DMF (10 mL) was treated under stirring with NaH (35 mg, 0.9 mmol, 60%) for 1 h at room temperature. After addition of ice water the mixture was extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with water (2 × 30 mL), dried (Na_2SO_4), and evaporated. Purification by column chromatography (toluene/acetone 2:1) and recrystallization from methanol yielded **5** (264 mg, 71%) as colorless needles; mp 259–262°C; $[\alpha]_D^{22}$ +182° (*c* 1.0, DMF); R_f 0.35 (toluene-acetone 2:1); IR (KBr): ν 3486, 3284 (NH_2), 1637 (C═C) cm^{-1}; ^1H NMR (250 MHz, [D_6]-DMSO): δ 3.57 (s, 3H, OMe), 3.91–4.09 (m, 2H, $J_{4',4a}$ 10.4 Hz, H-4′, H-4a), 4.40 (dd, 1H, $J_{4',4''}$ 9.2 Hz, $J_{4'',4a}$

3.7 Hz, H-4″), 5.01 (d, 1H, $J_{4a,11b}$ 7.6 Hz, H-11b), 5.93 (s, 1H, H-2), 6.00 (s, 1H, H-6), 6.88 (s, 2H, NH_2), 7.38–7.52 (m, 5H, Ph), 8.23 (s, 1H, H-9); ^{13}C NMR (63 MHz, [D_6]-DMSO): δ 54.8 (OMe), 64.7 (C-4a), 68.2 (C-4), 74.4 (C-11b), 94.9 (C-6), 101.3 (C-2), 112.9 (C-6b), 126.5 (Ph), 126.8 (C-6a), 128.4, 129.3 (Ph), 133.1 (C-11a), 137.3 (Ph), 154.1 (C-9), 158.3 (C-7), 166.9 (C-10a); MS (CI, isobutane): m/z (%) 372 (40) $[M + H]^+$, 107 (100).

Anal. Calcd for $C_{18}H_{17}N_3O_4S$: C, 58.21; H, 4.61; N, 11.31; S, 8.63. Found: C, 57.90; H, 4.69; N, 11.24; S, 8.74.

(2*R*,4a*R*,6*S*,9b*S*)-8-Amino-4a,6,9,9b-tetrahydro-6-methoxy-9-(4-methylphenyl-sulfonyl)-2-phenyl-4*H*-[1,3]dioxino[4′,5′:5,6]pyrano[4,3-*b*]pyrrole-7-carbonitrile (6). Triethylamine (0.09 mL, 0.65 mmol) was added at −20°C to a solution of **1** (200 mg, 0.64 mmol) and tosylazide (128 mg, 0.65 mmol) in acetonitrile (20 mL). Within 2 h the stirred mixture was allowed to warm up to +10°C and then poured into ice water (60 mL). After extraction with dichloromethane (3 × 20 mL) the combined organic layers were washed with water (3 × 20 mL), dried (Na_2SO_4), and concentrated to leave a syrup, which was purified by column chromatography (toluene/ethyl acetate 3:1). Recrystallization from dichloromethane/hexane furnished **6** (120 mg, 39%) as colorless crystals; mp > 150°C (decomposition); $[\alpha]_D^{21} + 26.9^\circ$ (*c* 1.0, $CHCl_3$); R_f 0.55 (toluene/ethyl acetate 4:1); IR (KBr): ν 3453, 3365 (NH_2), 2216 (CN) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.44 (s, 3H, Me), 3.50 (s, 3H, OMe), 3.91 (t, 1H, $J_{4',4''}$ 10.1 Hz, H-4′), 4.05–4.16 (m, 1H, $J_{4',4a}$ 10.1 Hz, H-4a), 4.31 (dd, 1H, $J_{4'',4a}$ 4.4 Hz, H-4″), 4.68 (d, 1H, $J_{4a,9b}$ 8.9 Hz, H-9b), 5.29 (s, 2H, NH_2), 5.58 (s, 1H, H-6), 5.70 (s, 1H, H-2), 7.29–7.91 (m, 9H, Ph, *p*-Me$C_6H_4SO_2$); ^{13}C NMR (75 MHz, [D_6]-acetone): δ 21.6 (Me), 60.0 (OMe), 65.4 (C-4a), 69.4 (C-4), 72.1 (C-7), 74.8 (C-9b), 95.8 (C-6), 102.0 (C-2), 114.5 (CN), 120.3 (C-6a), 123.0, 127.0, 128.6, 128.7, 129.4, 130.9, 135.5 (Ph, *p*-Me$C_6H_4SO_2$), 138.8 (C-9a), 147.5 (*p*-Me$C_6H_4SO_2$), 150.5 (C-8); (CI, isobutane): m/z (%) 482 (3) $[M + H]^+$, 107 (100).

Anal. Calcd for $C_{24}H_{23}N_3O_6S$: C, 59.86; H, 4.81; N, 8.73; S, 6.66. Found: C, 59.84; H, 5.03; N, 8.69; S, 6.87.

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