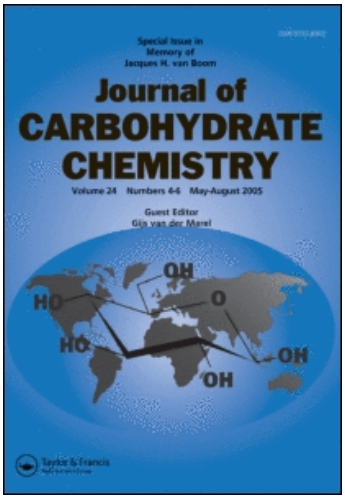

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Synthesis of *N*-Glycoside Analogs via Thionolactones[†]

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ABSTRACT

Indolyl *N*-glycoside analogs were obtained by a two-step sequence via indole *N*-thioamides. Treatment of thionobutyrolactone with indolylmagnesium bromide provides the corresponding indole *N*-thioamide. The use of 10:1 toluene:THF as solvent is important in favoring *N*- over *C*3-acylation. Treatment of the ω-hydroxy-thioamide with 2 equiv of Meerwein's reagent followed by sodium borohydride gives the corresponding *N*-(tetrahydrofuranyl)indole. Addition of carbon nucleophiles gives access to ketose nucleoside analogs, while activation of the ω-hydroxyl group can give access to tetrahydrothiophene *N*-glycosides.

Key Words: Azole *N*-thioamides; Thioacylation; Azole *N*-glycosides; Alkoxyiminium ions; Tetrahydrothiophene *N*-glycosides; Nucleoside analogs.

[†]This paper is dedicated to Professor Gérard Descotes on the occasion of his 70th birthday for his many contributions to carbohydrate chemistry.

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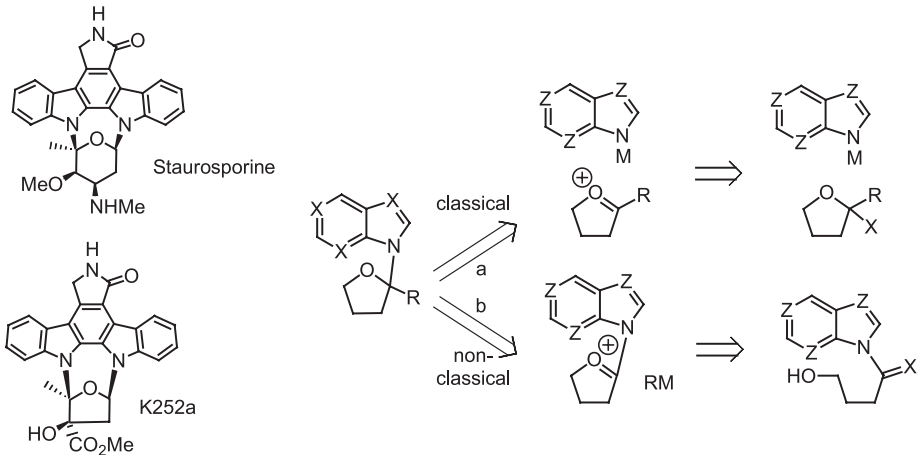
INTRODUCTION

The isolation of biologically active alkaloids having novel *N*-glycoside structures has led us to investigate new synthetic routes to *N*-glycosides.[1] The indolocarbazole bis-*N*-glycoside alkaloids such as staurosporine and K252a have generated significant synthetic and pharmaceutical interest.[2–7] These alkaloids bear two *N*-glycoside bonds, with a defined regiochemical relationship between the *N*-glycosides and the remote indolocarbazole lactam carbonyl. This aspect suggests a non-classical retrosynthetic disconnection of the exocyclic C–C or C–H bond of the *N*-glycoside, which leads to a carboxylic acid derivative (disconnection b, Scheme 1). The thioamide of an aromatic nitrogen heterocycle seems a viable candidate as starting material, based on pioneering work in the synthesis of *O*-glycosides via thioesters.[8,9] Extending these methodologies to the nitrogen series presents several interesting issues: creating the key C–N bond by acylation rather than glycosylation may provide important differences in regioselectivity and functional group compatibility; thioamides of azole heterocycles, whose fulvenoid character may lead to unusual reactivity, have not been studied extensively to our knowledge; finally, the rich chemistry of sulfur in nucleophilic, radical, single electron transfer, and transition–metal-catalyzed chemistry may provide access to novel structures and to new synthetic routes. The synthesis of simple indolyltetrahydrofurans from thionobutyrolactone as model *N*-glycosides is described herein.

RESULTS AND DISCUSSION

A variety of thioacylation conditions are available, although precedents for the specific case of azole heterocycles are rare.[10] The direct thioacylation of indole with a thionolactone is appealing in terms of synthetic efficiency, and in view of the fact that the corresponding thionolactones are known in the carbohydrate series (Scheme 2).[8,11] The addition of thionobutyrolactone[12] to a solution of indolylmagnesium bromide in



Scheme 1. Retrosynthetic disconnections for N-glycosides.

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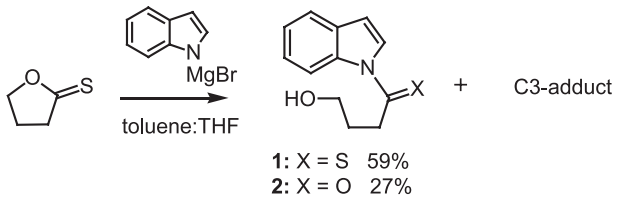


Scheme 2. Synthesis of indole w-hydroxythioamides.

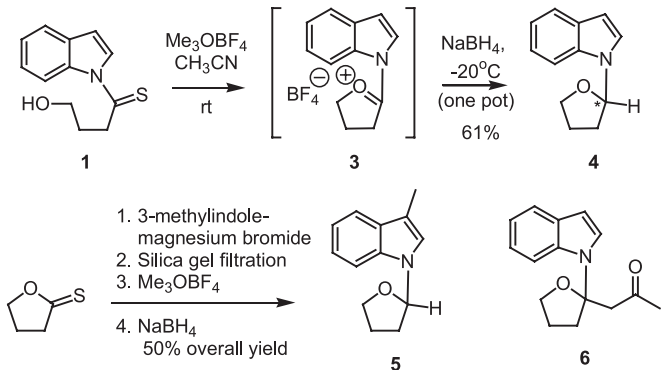
toluene led to the desired thioamide **1**, accompanied by the corresponding amide **2** and varying amounts of the C-3 adduct.[a] The thioamide shows characteristic NMR resonances at 208.5 ppm in the ^{13}C NMR (thiocarbonyl) and 9.11 ppm in the ^{1}H NMR (indole H-7, deshielded by the thiocarbonyl), while the amide shows corresponding resonances at 171.6 and 8.43 ppm, similar to those of *N*-acetylindole.[13]

The competition between N-1 and C-3 acylation of indole salts is well documented, and is dependent on the solvent and the nature of the metal salt[14] However, we found that the thioacylation was unsuccessful using other indole salts (Li, Na, K, or Cs), or in coordinating solvents such as THF. Nonetheless, we found that using a 10:1 mixture of toluene:THF suppressed the formation of the thioketone and gave an acceptable 59% yield of the thioamide **1**, accompanied by 27% of the corresponding amide **2**. Use of TMEDA or HMPA as additive was unsuccessful. We were unable to suppress the formation of the amide completely, either by using rigorously anhydrous experimental conditions or by changing the quench and workup conditions. An alternative approach to the thioamide consists of converting the amide **2** into the thioamide **1**. However, treatment of the amide with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent)[15,16] under standard conditions failed to produce even traces of the desired thioamide in our hands.

Several routes can be envisioned for converting the thioamide into an *N*-glycoside analog, and an efficient route is presented in Scheme 3. Treatment of the thioamide with 2 equiv of trimethyloxonium tetrafluoroborate (Meerwein's reagent)[17] leads to the alkoxyiminium ion **3**, via a sequence of alkylation, cyclization, alkylation, and elimination, which is then reduced in situ with sodium borohydride to give the *N*-glycoside model **4** in 61% yield. The proton NMR spectrum of **4** shows diastereotopic protons on the tetrahydrofuran ring, confirming the formation of a stereogenic center at C.1, and the EIMS matches that of the published spectrum.[18] The yield of the reaction is modest, yet acceptable in view of the complexity of the reaction sequence. An efficient protocol was developed, in which the thioamide was purified by silica gel filtration and carried on to the next step, giving a respectable 50% yield for the two-step conversion of thiobutyrolactone to the indolyltetrahydrofuran **5**.

Several exploratory experiments were undertaken to investigate other potential opportunities. Addition of carbon nucleophiles to the alkoxyiminium **3** gives access to

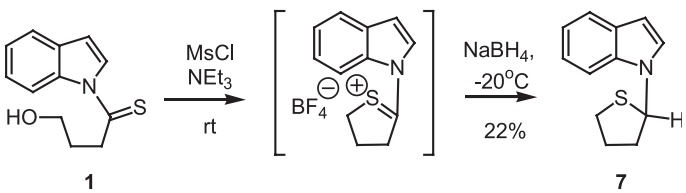
[a]The C3-thioketone adduct was isolated as a red, gummy, insoluble solid, which hydrolyzed spontaneously to the corresponding C3-ketone. The structure of the C3 ketone was assigned based on ^{1}H NMR alone.



Scheme 3. Synthesis of N-glycoside analogs from w-hydroxythioamides.

ketose nucleoside analogs. The thioamide **1** was treated with two equiv of Meerwein reagent, followed by a variety of carbon nucleophiles. Allylsilanes, allylstannanes, and hypervalent allyl silicates gave no addition, and the amide hydrolysis product was recovered after workup. Neither alkyllithiums, nor alkyl or allyl Grignard reagents, yielded the desired product. Ethylmagnesium bromide gave traces of a product identified as the ethyl adduct by proton NMR, but the reaction was not reproducible, presumably due to the instability of the product to the $MgBrBF_4$ produced in the reaction. Treatment of the alkoxyiminium ion **3** with trimethylsilyloxypropene gave the adduct **6** in 21% yield (Scheme 3). The poor yield in this case may be attributed to polymerisation of the enol ether in the presence of HBF_4 produced during the formation of the alkoxyiminium ion. This reaction was not pursued further on this system but these results demonstrate that electron-rich carbon nucleophiles can be added, although the alkoxyiminium ion is fairly unreactive.

Additional exploratory experiments were performed to determine whether activation of the hydroxyl group instead of the thiocarbonyl of the thioamide could give access to tetrahydrothiophenes (Scheme 4). Indeed, treatment of the thioamide **1** with methanesulfonyl chloride and triethylamine, followed by sodium borohydride gave the indolyltetrahydrothiophene **7**. The reaction was clean based on the ^1H NMR spectrum of the crude product, although the isolated yield was poor. The sequence of addition of the reagents (sulfonyl chloride followed by the base) was essential, as the thioamide is unstable to basic conditions. Stronger bases (e.g., DBU) gave only decomposition, while weak bases (e.g., lutidine, 1 equiv DMAP) or the absence of base gave the



Scheme 4. Synthesis of tetrahydrothiophenes from w-hydroxythioamides.

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tetrahydrofuran (S-activation). The appropriate balance must be found, and acceptable results may be obtained in systems in which the thioamide is less electrophilic.

We have demonstrated that indolylmagnesium bromides can be thioacylated regioselectively with thionolactones in THF:toluene mixtures, and that these thioamides can be converted to aldose, ketose, and tetrahydrothiophene nucleoside analogs. The current system is structurally very simple, yet presents, in our opinion, certain interesting features of azole thioamides and alkoxyiminium salts. This methodology may offer a complementary approach in cases where traditional *N*-glycosylation is unsuitable for reasons of regiochemistry, stereochemistry, or chemoselectivity. The application of this methodology to carbohydrate thiolactones is currently under investigation.

EXPERIMENTAL

General methods. General experimental procedures were described previously.[19] NMR spectra were collected on a General Electric QE-300 spectrometer, low- and high-resolution mass spectra were obtained using a JEOL AX-505H or a JEOL SX-102A spectrometer. NMR assignments are interpreted based on literature precedents,[20,21] and on $^{1}H-^{13}C$ HSQC data for compound **4**.

4-Hydroxy-1-indol-1-yl-butane-1-thione (1) and 4-hydroxy-1-indol-1-yl-butane-1-one (2). A stirred solution of indole (275 mg, 2.35 mmol) in toluene:THF (10:1 4.4 mL) at 45°C under N_2 was treated with ethylmagnesium bromide (3M in diethyl ether, 0.8 mL, 2.4 mmol), and the mixture was stirred for 20 min. Freshly distilled γ-butyrothiolactone[12] (110 μL, 120 mg, 1.18 mmol) was added and an off-white precipitate was observed immediately. The mixture was stirred for 20 min, cooled to rt, and poured into an aq solution of HCl (0.5N, 4 mL). The mixture was diluted with ether and washed with brine (3 × 30 mL). The individual aqueous layers were back-extracted with ether, and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was applied to a 2 × 2 cm silica gel column on a sintered glass funnel and eluted with CH_2Cl_2, to provide thioamide **1** (yellow oil, 151 mg, 0.688 mmol, 59% yield) and amide **2** (colorless oil, 63.5 mg, 0.312 mmol, 27% yield). **1**: IR (cm^{-1}): 3344 (O–H), 3065 (Ar C–H), 2980 (C–H), 2872 (C–H), (no C═O) ^{1}H NMR ($CDCl_3$): δ 9.11 ppm (1H, d, J = 8.2 Hz, H-7), 7.86 (1H, d, J = 3.9 Hz, H-2), 7.55 (1H, dd, J = 7.0, 1.0 Hz, H-4), 7.23–7.36 (2H, H-5/H-6), 6.70 (1H, d, J = 3.8 Hz, H-3), 3.76 (2H, t, J = 5.8 Hz, H-4′), 3.47 (2H, t, J = 7.6 Hz, H-2′), 2.16 (2H, m, H-3′). ^{13}C NMR (C_6D_6): δ 208.5 ppm (C1′═S), 138.0 (7a), 132.8 (3a), 127.5 (C2), 126.4 (C6), 125.3 (C4), 121.7 (C5), 118.8 (C7), 110.6 (C3), 61.5 (C4′), 45.0 (C2′), 32.8 (C3′). LRMS(EI): *m/z* 219 (12, M^+), 185 (47, $M-H_2S$), 117 (100, indole$^+$), 111 (23). HRMS(EI). *m/z* calcd for $C_{12}H_{13}NOS$: 219.0718. Found 219.0720.

2: IR (cm^{-1}): 3344 (O–H), 3066 (Ar C–H), 2931 (C–H), 2878 (C–H), 1695 (C═O). ^{1}H NMR ($CDCl_3$): δ 8.43 ppm (1H, d, J = 8.2 Hz, H-7), 7.54 (1H, d, J = 8.2 Hz, H-4), 7.45 (1H, d, J = 3.8 Hz, H-2), 7.30–7.36 (1H, dd, J = 7.2, 8.2 Hz, H-5), 7.26 (1H, dd, J = 7.2, 8.2 Hz, H-6), 6.60 (1H, d, J = 4.9 Hz, H-3), 3.76 (2H, t, J = 5.9 Hz, H-4′), 3.01 (2H, t, J = 7.0 Hz, H-2′), 2.06 (2H, m, H-3′). ^{13}C NMR ($CDCl_3$): δ 171.6 ppm (C1′═O), 135.5 (C7a), 130.3 (C3a), 125.0 (C2), 124.6 (C6), 123.6 (C4), 120.8 (C5), 116.5 (C7), 109.2 (C3), 61.1 (C4′), 32.3 (C2′), 27.2 (C3′). LRMS(EI): *m/z* 203

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(18, M^+), 117 (100, indole$^+$), 97 (28). HRMS(EI). *m/z* calcd for $C_{12}H_{13}NO_2$: 203.0946. Found 203.0946.

***N*-[Tetrahydrofuran-2-yl]-1*H*-indole (4).**[18] A stirred solution of the thioamide **1** (60 mg, 0.274 mmol) in dry acetonitrile (0.8 mL) at rt under N_2 was treated with a solution of trimethyloxonium tetrafluoroborate (Meerwein's reagent, 80 mg, 0.55 mmol) in acetonitrile (0.5 mL). The mixture was stirred for 5 min and cooled to −20°C. Solid $NaBH_4$ (excess) was added and the mixture was allowed to warm to rt over a period of 1 h. The reaction was quenched with methanol and the solvents were removed in vacuo. The mixture was diluted with ether and washed 3 times with brine. The aq layers were back-extracted with ether and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Silica gel chromatography (20%, 50%, 100% CH_2Cl_2:hexane, diethyl ether) gave the tetrahydrofuran indole **4**[18] as a clear colorless oil (31 mg, 0.166 mmol, 61% yield). IR (cm^{-1}): 3067 (Ar C−H), 2945 (C−H), 1183 (C−O). ^{1}H NMR ($CDCl_3$): δ 7.62 ppm (1H, dd, J = 7.7, 0.8 Hz, H-7), 7.46 (1H, dd, J = 8.2, 0.7 Hz, H-4), 7.25−7.19 (2H, H-2/H-6), 7.12 (1H, dd, J = 7.6, 7.6 Hz, H-5), 6.53 (1H, d, J = 3.4 Hz, H-3), 6.25 (1H, dd, J = 6.0, 4.4 Hz, H-2′), 4.13 (1H, ddd, J = 8.4, 7.5, 6.0 Hz, H-5′a), 3.98 (1H, ddd, J = 8.4, 7.1, 6.9 Hz, H-5′b), 2.39 (2H, m, H-4′), 2.17 (2H, m, H-3′). ^{13}C NMR ($CDCl_3$): δ 135.7 ppm (C7a), 129.2 (C3a), 124.0 (C2), 121.8 (C6), 120.9 (C4), 119.9 (C5), 110.0 (C7), 102.3 (C3), 85.8 (C2′), 68.3 (C5′), 31.6 (C4′), 24.8 (C3′). LRMS(EI): *m/z* 187 (12, M^+), 117 (100, indole$^+$), 71(38, $C_4H_7O^+$).

3-Methyl-*N*-[tetrahydrofuran-2-yl]-1*H*-indole (5). 3-Methylindolemagnesium bromide (3.2 mmol) in 10:1 toluene:THF (5.5 mL) was treated with thiobutyrolactone (150 μL, 1.60 mmol) according to the procedure above. The crude product after aqueous workup was applied in CH_2Cl_2:toluene (1:1) to a pad of silica gel on a sintered glass funnel, and eluted with CH_2Cl_2 until the yellow color was near the bottom of the pad. The pad was eluted with EtOAc, and the crude product from EtOAc was azeotroped from toluene (3 ×), and reacted with Meerwein reagent and $NaBH_4$ as above, to yield, after silica gel chromatography (CH_2Cl_2 eluant), the 3-methylindole adduct **5** as a clear colorless oil (160.8 mg, 0.797 mmol, 50% yield from thiobutyrolactone). IR (cm^{-1}): 3052 (ArC−H), 2956 (C−H), 2918 (C−H), 2880 (C−H), 1455 (C═C), 1052 (C−O). ^{1}H NMR ($CDCl_3$): δ 7.53 ppm (1H, d, J = 7.6 Hz, H-7), 7.39 (1H, d, J = 8.1 Hz, H-4), 7.18 (1H, ddd, J = 8.1, 7.0, 0.9 Hz, H-5), 7.10 (1H, ddd, J = 7.8, 7.1, 0.9 Hz, H-6), 6.92 (1H, s, H-2), 6.10 (1H, dd, J = 5.6, 5.1 Hz, H-2′), 4.03 (1H, ddd, J = 8.3, 7.5, 6.0 Hz, H-5′a), 3.87 (1H, ddd, J = 8.3, 7.3, 6.6 Hz, H-5′b), 2.36−2.17 (2H, m, H-4′ab), 2.31 (3H, s, C3−C*H*$_3$), 2.17−1.90 (2H, m, H-3′ab). ^{13}C NMR ($CDCl_3$): δ 136.0 ppm (s, C7a), 129.2 (s, 3a), 121.6 (d, C2 or C6), 121.4 (d, C6 or C2), 119.1 (d, C4), 118.8 (d, C5), 111.3 (s, C3), 109.6 (d, C7), 85.2 (d, C2′), 67.9 (t, C5′), 31.1 (t, C3′), 24.7 (t, C2′), 9.5 (q, C3−*C*H$_3$). HRMS(EI). *m/z* calcd for $C_{13}H_{15}NO$: 201.1154. Found: 201.1155 LRMS(EI): *m/z* 201(34, M^+), 131(100, 3-methylindole), 71(30, $C_4H_7O^+$), 43(60, $C_2H_3O^+$).

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51,N 6.96. Found: C, 77.81 H, 7.67,N 6.98.

1-[2′-(1-Indolyl)tetrahydrofuran-2-yl]-2-propanone (6). A stirred solution of the thioamide **1** (34 mg, 0.155 mmol) in dry acetonitrile (0.2 mL) at rt under N_2 was treated with a solution of Meerwein's reagent (45 mg, 0.31 mmol) in acetonitrile (0.8 mL), and the mixture was stirred for 20 min. The mixture was cooled to −20°C and 2-trimethylsilyloxypropene (200 μL, 1.02 mmol) was added to the frozen reaction

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mixture. The reaction was allowed to rise to 0°C over a period of 1 h, and the reaction was quenched with brine. The mixture was extracted with diethyl ether and washed with brine 3 times. The aqueous layers were back-extracted with ether and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Silica gel chromatography (CH_2Cl_2 eluant) gave the ketose nucleoside analog **6** as a clear colorless oil (8.0 mg, 0.033 mmol, 21% yield). IR (cm^{-1}): 3067 (Ar C–H), 2983 (C–H), 2945 (C–H), 1730 (C═O), 1184 (C–O). ^{1}H NMR ($CDCl_3$): δ 7.61 ppm (1H, d, J = 7.4 Hz, H-7″), 7.30 (1H, d, J = 3.4 Hz, H-2″), 7.22–7.09 (3H, H-4″, H-5″, H-6″), 6.47 (1H, d, J = 3.3 Hz, H-3″), 4.11 (1H, ddd, J = 8, 7, 6 Hz, H-5′a), 3.97 (1H, ddd, J = 7, 7, 7 Hz, H-5′b), 3.31 (1H, d, J = 14.3 Hz, H-1a), 3.18 (1H, d, J = 14.3 Hz, H-1b), 2.90 (1H, ddd, J = 13.1, 7.8, 3.9 Hz, H-3′a), 2.45 (1H, ddd, J = 13.1, 9.0, 9.0 Hz, H-3′b), 2.05 (1H,m H-4′a), 1.95 (3H, s, C2(O)C*H*$_3$), 1.91 (1H, m, H-4′b). ^{13}C NMR ($CDCl_3$): δ 205.5 ppm (C2═O), 136.8 (C7″a), 130.3 (C3″a), 125.2 (C2″), 121.6 (C6″), 121.1 (C4″), 119.7 (C5″), 112.4 (C7″), 101.6 (C3″), 95.6 (C2′), 68.4 (C5′), 51.2 (C1), 36.1 (C3′), 31.6 (C4′), 21.5 (C3). LRMS(EI): *m*/*z* 243 (23, M^+), 117 (100, indole). HRMS(EI). *m*/*z* calcd for $C_{15}H_{17}NO_2$: 243.1259. Found 243.1261.

***N*-[Tetrahydrothiophen-2-yl]-1*H*-indole (7).** A stirred solution of thioamide **1** (15 mg, 0.068 mmol) in dry acetonitrile (0.8 mL) at rt under N_2 was treated with methanesulfonyl chloride (8 μL, 0.11 mmol) followed by triethylamine (9 μL, 0.07 mmol). The mixture was stirred at rt for 15 min and solid $NaBH_4$ (excess) was added. Aqueous workup and silica gel chromatography (1:2 CH_2Cl_2:hexanes, then CH_2Cl_2) provided the tetrahydrothiophene **7** (3.0 mg, 0.015 mmol, 22% yield). ^{1}H NMR ($CDCl_3$): δ 7.61 ppm (1H, d, J = 7.9 Hz, H-7), 7.49 (1H, d, J = 3.3 Hz, H-2), 7.42 (1H, d, J = 8.2 Hz, H-4), 7.22 (1H, dd, J = 8.2, 7.1 Hz, H-5), 7.12 (1H, dd, J = 7.9, 7.1 Hz, H-6), 6.52 (1H, d, J = 3.4 Hz, H-3), 6.21 (1H, dd, J = 6.0, 4.4 Hz, H-2′), 3.28 (1H, m, H-5′a), 3.01 (1H, m, H-5′b), 2.36 (2H, m, H-3′), 2.18 (2H, m, H-4′). LRMS(EI): *m*/*z* 205 (4, $[M + 2]^+$), 204 (9, $[M + 1]^+$), 203 (56, M^+), 117 (100, indole$^+$). HRMS(EI). *m*/*z* calcd for $C_{12}H_{13}NS$: 203.0769. Found 203.0767.

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