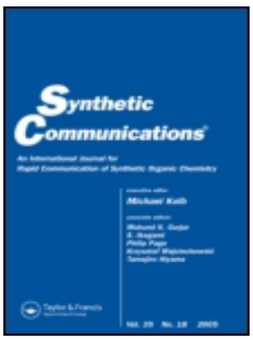

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FORMAL SYNTHESIS OF CYTOSAMINE— A COMPONENT OF NUCLEOSIDE ANTIBIOTICS, THE AMICETIN FAMILY

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ABSTRACT

A facile route to a synthetic precursor of the nucleoside antibiotics, amicetins, was investigated employing stable phenyl thioglycosides as key building blocks.

Cytosamine is a common skeleton of the amicetin group of antibiotics produced in the fermentation broth of various species of *Streptomyces* and *Aethrobacter*.[1] The structure features the presence of a unique deoxyhexopyranosyl nucleoside in which the 4′-hydroxyl group is glycosylated by an amino sugar called amosamine.

Amicetin was isolated in the early 1950s by several groups,[2–5] and the correct structure was established in 1963 by Stevens et al.[6] Totally about ten disaccharide nucleosides having closely related structures have been found to date.[7–12] The latest example is the cytosaminomycins which were isolated as anticoccidial agents from a species of *Streptomyces* obtained from a soil sample.[12]

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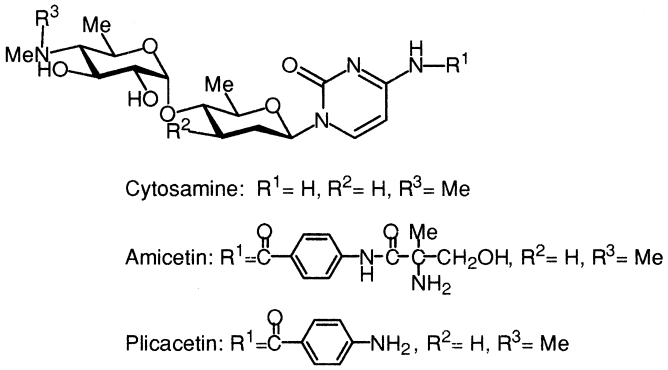

Figure 1. Structure of the amicetin family antibiotics.

The synthetic study of these antibiotics is significantly important in order to not only elucidate their relation between the structures and biological properties but also to design novel artificial molecules related to these antibiotics. However, only one total synthesis of such a nucleoside antibiotic, plicacetin—one of the simplest disaccharide nucleosides of the amicetin family, has been accomplished by Stevens et al. in 1972.[13]

Recently, we developed a stereoselective route to a trideoxyhexopyranosyl nucleoside,[14] which corresponds to the component of cytosamine, as part of our ongoing search to establish intramolecular glycosylation for nucleoside synthesis.[15] Alternatively, the recent progress in methodologies for the synthesis of complex oligosaccharides prompted us to develop more facile routes to amicetin family antibiotics. In this paper, we describe a formal synthesis of cytosamine via coupling of the above-obtained hexopyranosyl nucleoside and an amosamine equivalent using stable thioglycosides as key building blocks.

The route to thioglycoside **6**, a synthetic equivalent of amosamine, is shown in Scheme 1. Starting from commercially available penta-*O*-acetyl-β-D-galactopyranose, phenyl 1-thiogalactopyranoside (**2**) was prepared according to a reported procedure[16] with slight modifications. Protection of the 4- and 6-hydroxyls with a benzylidene group was followed by benzylation of the 2,3-hydroxyls to afford fully protected thioglycoside **3** in 83% overall yield. The 4,6-*O*-benzylidene was removed under acidic conditions to provide diol **4**, whose primary hydroxyl group underwent selective tosylation, followed by reduction with lithium triethylborohydride,[17] yielding 6-deoxy derivative **5**. Finally, substitution of the 4-hydroxyl with azide via a 4-*O*-mesyl derivative was accomplished in a general manner to afford the requisite thioglycoside **6** in a total good yield.

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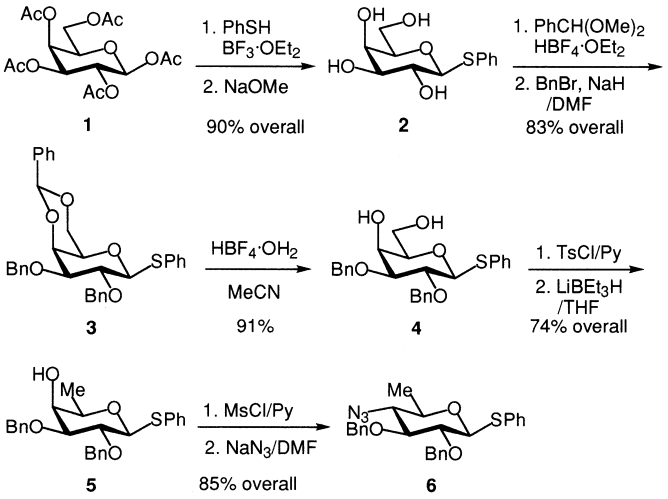

Scheme 1. Preparation of the glycosyl donor.

With the amosamine-type glycosyl donor in hand, we next investigated the glycosylation reaction of 2′,3′,6′-trideoxy-β-D-*erythro*-hexopyranosyl nucleoside **8**.[15] To date, numerous methods have been reported for glycoside synthesis.[18] However, selective formation of α-*gluco*-type glycosides using thioglycosides as the glycosyl donor is still limited. Fukase et al. have reported that the use of an NBS-$LiClO_4$ combination for activation of thioglycosides furnished α-glycosides.[19] However, when we employed this activation system for the coupling between nucleoside **8** and thioglycoside **6**, the reaction did not take place and only the starting materials were recovered. Alternatively, treatment of **8** and **6** with $Me_2S(SMe)BF_4$ as the activator led to the desired nucleoside disaccharide, although the yield and the selectivity regarding the anomeric center were not satisfactory (16%, $\alpha/\beta = 2$).

As is well-known, thioglycosides can be converted into glycosyl fluorides, on treatment of NBS-DAST or NBS-HF·Py, which serve as powerful glycosylating agents in the presence of a silver salt and tin(II) chloride. For instance, reaction of a benzyl-protected D-galactopyranosyl fluoride activated by AgOTf-$SnCl_2$ in Et_2O gave an α-galactosylated product with high selectivity.[20] We therefore applied this system to the synthesis of the disaccharide nucleoside. Treatment of thioglycoside **6** with NBS-HF·Py afforded a glycosyl fluoride **7** in 95% yield ($\alpha/\beta =$ ca.2). Subsequently, the reaction of the glycosyl fluoride **7** with nucleoside **8** was promoted by AgOTf-$SnCl_2$ (5 equiv.) in the presence of MS 4A in Et_2O-dichloroethane (9:1) at room temperature for 40 h to furnish the desired α-anomer of the

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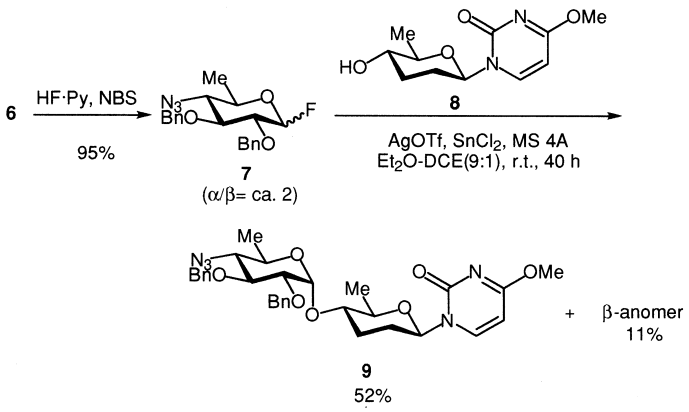

Scheme 2. Synthesis of the disaccharide nucleoside.

disaccharide nucleoside **9** in 52% isolated yield along with its β-anomer (11%) and recovery of unreacted nucleoside (11%). Both prolonged reaction and increased amounts of activator did not lead to improvement in the yield of the product or complete consumption of the starting nucleoside.

The anomeric configuration of the α-anomer **9** was confirmed by ^{1}H NMR analysis. The anomeric proton appeared as a doublet at δ 4.84 with $J = 3.4$ Hz and indicated an equatorial proton. By contrast, that of the β-anomer appeared at 4.42 ppm with $J = 7.3$ Hz, indicating an axial proton.

The disaccharide nucleoside **9** has a closely related structure that has been synthesized by Stevens et al. and could be converted into cytosamine itself.[13] Hence, we accomplished a formal synthesis of cytosamine here.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were obtained on a JEOL JNM-EX400 spectrometer in $CDCl_3$ with Me_4Si as an internal standard. *J* Values are given in Hz. IR spectra were recorded on a Perkin-Elmer Model 1600 spectrophotometer. TLC was performed on plates coated with silica gel 60 F_{254} (Merck). For column chromatography, Wakogel C-300 (Wako Chemicals) was used. All solvents used in the reactions were distilled from an appropriate drying agent and stored over molecular sieves.

Phenyl 1-thio-β-D-galactopyranoside (**2**). To a solution of 1,2,3,4,6-penta-*O*-acetyl-D-galactose (**1**) (10.0 g, 25.6 mmol) and PhSH (3.2 ml, 31 mmol) in CH_2Cl_2 (50 mL) under Ar was added $BF_3{\cdot}OEt_2$ (15.7 mL,

128 mmol) at room temperature. The reaction mixture was stirred for 6 h and then poured into saturated aqueous $NaHCO_3$ solution. The organic layer was separated, dried, and concentrated. The residue was purified by flash chromatography (hexane-AcOEt, 2:1) to provide phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (10.94 g, 97%). ^{1}H NMR δ 1.97 (s, 3H), 2.04 (s, 3H), 2.09 (s, 3H), 2.12 (s, 3H), 3.98 (dt, 1H, $J = 5.9, 13.2$), 4.21 (dd, 1H, $J = 4.4, 11.2$), 4.77 (dt, 1H, $J = 5.9, 15.6$), 5.08 (dd, 1H, $J = 3.4, 15.6$), 5.28 (dt, 1H, $J = 4.4, 5.9, 15.6$), 5.46 (d, 1H, $J = 3.4$), 7.11–7.36 (m, 5H). To a solution of this thiogalactoside (6.72 g, 15.3 mmol) in MeOH (100 mL) was added 30% NaOMe solution (8.4 mL) at 0°C. The reaction mixture was stirred for 20 min at the same temperature and then neutralized with DOWEX 50W (H^+-form). After removal of the resin by filtration, concentration of the filtrate afforded phenyl 1-thio-β-D-galactopyranoside (**2**) (3.85 g, 93%). ^{1}H NMR δ 2.05–2.17 (m, 1H), 2.48–2.49 (m, 1H), 2.68–2.80 (m, 1H), 3.49 (d, 1H, $J = 15.6$), 3.61–3.72 (m, 2H), 4.57 (d, 1H, $J = 9.3$), 7.25–7.36 (m, 5H). Anal. Calcd. for $C_{12}H_{16}O_5S$: C, 52.93; H, 5.92. Found: C, 52.53; H, 6.07.

Phenyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-galactopyranoside (**3**). According to the literature,[21] thiogalactopyranoside (**2**) (3.85 g, 14.2 mmol) was treated with benzaldehyde dimethylacetal (2.3 mL, 15.3 mmol) and tetrafluoroboric acid etherate (2.1 mL, 14.3 mmol) in DMF (140 mL) for 7 h at room temperature. After addition of Et_3N (2.0 mL, 14.3 mmol), the mixture was evaporated under reduced pressure. The residue was purified by flash chromatography (hexane-AcOEt, 2:1) to provide phenyl 4,6-*O*-benzylidene-1-thio-β-D-galactopyranoside (4.31 g, 84%). ^{1}H NMR δ 2.46–2.56 (m, 2H), 2.88 (d, 1H, $J = 15.1$), 2.99 (d, 1H, $J = 15.1$), 3.70–3.72 (m, 3H), 4.24–4.54 (m, 4H), 5.53 (d, 1H, $J = 15.1$), 7.26–7.71 (m, 10H). To a solution of phenyl 4,6-*O*-benzylidene-1-thio-β-D-galactopyranoside (4.31 g, 12.0 mmol) in DMF (120 mL) was added NaH (60% in mineral oil, 1.43 g, 36.0 mmol). After 1 h, benzyl bromide (3.6 mL, 30 mmol) was added to the reaction mixture, and stirring was continued overnight. The reaction was quenched by addition of MeOH. The mixture was neutralized with saturated aqueous NH_4Cl solution and then extracted with $CHCl_3$. The organic layer was washed with water several times, dried, and concentrated. The residue was purified by flash chromatography (hexane/EtOAc, 2:1) to afford **3** (6.42 g, 99%). ^{1}H NMR δ 3.45 (d, 1H, $J = 1$), 3.63 (dd, 1H, $J = 3.4, 9.3$), 3.90 (t, 1H, $J = 9.3$), 4.01 (dd, 1H, $J = 1.5, 10.7$), 4.16 (d, 1H, $J = 2.9$), 4.38 (dd, 1H, $J = 1.5, 10.7$), 4.62 (d, 1H, $J = 9.8$), 4.65–4.76 (m, 4H), 5.49 (s, 1H), 7.15–7.45 (m, 16H), 7.50–7.55 (m, 2H), 7.71 (d, 1H, $J = 6.8$); IR (KBr) 2864, 1453, 1367, 1168, 1092, 1058, 1027 cm^{-1}. Anal. Calcd for $C_{33}H_{32}O_5S$: C, 73.31; H, 5.97. Found: C, 73.21; H, 5.93.

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Phenyl 2,3-di-*O*-benzyl-1-thio-β-D-galactopyranoside (4). According to the literature,[21] **3** (322 mg, 0.6 mmol) was treated with tetrafluoroboric acid (48%wt. in water, 0.09 mL) in MeCN (12 mL) at room temperature overnight. After addition of Et_3N (0.2 mL), the mixture was evaporated under reduced pressure. The residue was dissolved in $CHCl_3$, which was washed with saturated aqueous $NaHCO_3$ solution. The organic layer was dried, concentrated, and purified by flash chromatography (hexane/EtOAc, 1:1) to afford **4** (244 mg, 91%). ^{1}H NMR δ 2.85 (br, 1H), 2.96 (br, 1H), 3.43 (t, 1H, $J = 5.4$), 3.54 (dd, 1H, $J = 2.9$, 8.8), 3.71–3.80 (m, 2H), 3.90 (dd, 1H, $J = 6.4$, 11.8), 4.03 (d, 1H, $J = 2.9$), 4.63 (d, 1H, $J = 9.8$), 4.64 (d, 1H, $J = 11.7$), 4.68 (d, 1H, $J = 11.7$), 4.72 (d, 1H, $J = 10.3$), 4.80 (d, 1H, $J = 10.3$), 7.15–7.45 (m, 13H), 7.50–7.58 (m, 2H); IR (KBr) 3406, 2870, 1454, 1363, 1078 cm^{-1}. Anal. Calcd for $C_{26}H_{28}O_5S$: C, 69.00; H, 6.24. Found: C, 68.84; H, 6.24.

Phenyl 2,3-di-*O*-benzyl-6-deoxy-1-thio-β-D-galactopyranoside (5). To a solution of **4** (1.02 g, 2.25 mmol) in pyridine (20 mL) was added *p*-toluenesulfonyl chloride (0.644 g, 3.38 mmol) at 0°C. The reaction mixture was stirred at room temperature overnight and then quenched with water. The mixture was extracted with $CHCl_3$ three times. The combined organic layer was dried, concentrated, and purified by flash chromatography (hexane/EtOAc, 2:1) to afford 6-*O*-tosyl ester (1.15 g, 85%). The tosylate (0.558 g, 0.92 mmol) was dissolved in THF (2 mL) under Ar. Lithium triethylborohydride (1 M in THF, 3 mL) was added, and stirring was continued for 3 h. Hydrogen peroxide (30%, 3 mL) was added dropwise at 0°C, and the mixture was then allowed to warm to room temperature and was extracted with $CHCl_3$. After drying and concentration of the organic layer, the residue was purified by flash chromatography (hexane/EtOAc, 4:1) to afford **5** (0.348 g, 87%) as a syrup. ^{1}H NMR δ 1.37 (d, 3H, $J = 6.3$), 2.28 (d, 1H, $J = 2.6$), 3.52–3.62 (m, 2H), 3.69 (t, 1H, $J = 9.2$), 3.81–3.86 (m, 1H), 4.60 (d, 1H, $J = 9.9$), 4.71 (s, 2H), 4.74 (d, 1H, $J = 10.2$), 4.83 (d, 1H, $J = 10.2$), 7.15–7.45 (m, 13H), 7.50–7.59 (m, 2H); IR (KBr) 3430, 1365, 1130, 1085, 1057 cm^{-1}. Anal. Calcd for $C_{26}H_{28}O_4S$: C, 71.53; H, 6.46. Found C, 71.54; H, 6.59.

Phenyl 4-*C*-azido-2,3-di-*O*-benzyl-4,6-dideoxy-1-thio-β-D-glucopyranoside (6). To a solution of **5** (0.254 g, 0.582 mmol) in pyridine (3 mL) was added methanesulfonyl chloride (0.14 mL, 1.75 mmol) at 0°C. The reaction mixture was stirred at the same temperature for 2 h and then quenched with water. The mixture was extracted with ether several times and the combined organic layer was washed with dil. HCl, water, and saturated aqueous $NaHCO_3$ solution. Drying and concentration of the organic layer gave the crude 4-*O*-mesyl ester. This was dissolved in DMF (6 mL), and sodium azide (0.189 g, 2.91 mmol) was then added to the solution. The reaction mixture was stirred at 100°C for 7 h. After cooling, the mixture was diluted with ether. The organic layer was washed with water, dried, and concentrated.

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The residue was purified by TLC (hexane/EtOAc, 19:1) to afford **6** (0.208 g, 77%). ^{1}H NMR δ 1.39 (d, 1H, $J = 5.9$), 3.15–3.27 (m, 2H), 3.44–3.58 (m, 2H), 4.62 (d, 1H, $J = 9.2$), 4.72 (d, 1H, $J = 10.2$), 4.83 (d, 1H, $J = 10.6$), 4.88 (d, 1H, $J = 10.6$), 4.92 (d, 1H, $J = 10.2$), 7.20–7.46 (m, 13H), 7.46–7.60 (m, 2H); IR (KBr) 2108, 1454, 1358, 1274, 1129, 1094, 1043, 1028 cm^{-1}. Anal. Calcd for $C_{26}H_{27}N_3O_3S$: C, 67.66; H, 5.90. Found: C, 67.66; H, 5.96.

Disaccharide nucleoside 9. To a solution of thioglycoside **6** (73.0 mg, 0.158 mmol) in CH_2Cl_2 (2 mL) was added an HF-pyridine complex (0.16 mL) followed by *N*-bromosuccinimide (31 mg, 0.17 mmol) at –35°C. The mixture was allowed to warm to 0°C over 1 h. The reaction mixture was diluted with EtOAc and poured into saturated aqueous $NaHCO_3$ solution. The organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine, dried, and concentrated. The residue was purified by flash chromatography (hexane-EtOAc, 19:1) to afford glycosyl fluoride **7** (56.0 mg, 95%). The fluoride was obtained as a 2:1 (α/β) mixture of anomers and was used for the following step without separation.

To a suspension of AgOTf (167 mg, 0.65 mmol), $SnCl_2$ (123 mg, 0.65 mmol), and crushed 4-A molecular sieves (200 mg) in ether (4 mL) was added nucleoside **8**[15] (31.2 mg, 0.13 mmol) in ether (2 mL) and 1,2-dichloroethane (1 mL) at 0°C. After stirring for 5 min, glycosyl fluoride **7** (72.6 mg, 0.195 mmol) in ether (2 mL) was added, and stirring was continued at room temperature for 40 h. The reaction mixture was diluted with EtOAc and filtered through Celite. The filtrate was washed with aqueous $NaHCO_3$ solution and brine. The organic layer was dried and concentrated. The residue was purified by TLC (hexane-EtOAc, 1:1) to afford **9** (40.2 mg, 52%), accompanied by its β-anomer (8.2 mg, 11%) and the starting nucleoside **8** (11%). Compound **9**: $[\alpha]_D^{25} + 192^\circ$ (*c* 1.26, $CHCl_3$); ^{1}H NMR δ 1.26 (d, 3H, $J = 6.4$), 1.32 (d, 3H, $J = 6.4$), 1.34–1.45 (m, 1H), 1.57–1.71 (m, 1H), 2.13–2.21 (m, 1H), 2.26–2.33 (m, 1H), 3.10 (t, 1H, $J = 9.8$), 3.30 (ddd, 1H, $J = 2.9$, 4.4, 10.7), 3.53–3.63 (m, 2H), 3.73–33.83 (m, 2H), 3.96 (s, 3H), 4.60 (d, 1H, $J = 11.7$), 4.75 (d, 1H, $J = 11.7$), 4.81 (d, 1H, $J = 10.3$), 4.84 (d, 1H, $J = 3.4$), 4.95 (d, 1H, $J = 10.3$), 5.78 (dd, 1H, $J = 2.0$, 10.3), 5.92 (d, 1H, $J = 7.3$), 7.25–7.45 (m, 10H), 7.69 (d, 1H, $J = 7.3$); ^{13}C NMR δ 18.4, 18.8, 26.5, 30.5, 54.5, 66.6, 67.9, 73.5, 73.9, 75.7, 76.8, 79.6, 89.8, 82.9, 92.9, 95.8, 127.9, 128.0, 128.2, 128.3, 128.4, 128.6, 137.7, 137.9, 142.2, 155.3, 171.6. Anal Calcd for $C_{31}H_{37}N_5O_7$: C, 62.93; H, 6.30. Found: C, 62.92; H, 6.36. β-Anomer of **9**: ^{1}H NMR δ 1.30 (d, 3H, $J = 6.4$), 1.33 (d, 3H, $J = 5.9$), 1.41–1.65 (m, 1H), 1.83 (ddd, 1H, $J = 3.9$, 11.2, 13.2), 2.16–2.34 (m, 1H), 3.08–3.31 (m, 3H), 3.39–3.51 (m, 2H), 3.60–3.69 (m, 1H), 3.96 (s, 3H), 4.42 (d, 1H, $J = 7.3$), 4.73 (d, 1H, $J = 10.7$), 4.79 (d, 1H, $J = 10.7$), 4.88 (d, 1H, $J = 10.7$), 4.90 (d, 1H, $J = 10.7$), 5.77 (dd, 1H, $J = 2.0$, 10.3), 5.91 (d, 1H, $J = 7.3$), 7.22–7.40 (m, 10H), 7.66 (d, 1H, $J = 7.3$).

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