Total Synthesis of Cytosaminomycin C

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The first synthesis of cytosaminomycin C has been accomplished by employing intramolecular glycosylation for the β-selective formation of the 2′-deoxyhexopyranosyl nucleoside part as a key reaction.

Cytosaminomycins A–D are novel anticoccidial antibiotics isolated from the cultured broth of *Streptomyces amakusaensis* KO-8119.[1] The structure, closely related to the amicetin family antibiotics, features the presence of a unique 1-(2,6-dideoxyhexopyranosyl)cytosine in which the 4′-hydroxy is glycosylated by an amino sugar called amosamine (Figure 1). Amicetin was first isolated in the early 1950s by several groups,[2–5] and the correct structure was established in 1963 by Steavens et al.[6] To date, structurally related disaccharide nucleosides have been found by several groups,[7–11] and the cytosaminomycin is the most recent entry in this group. The synthetic study of these disaccharide nucleosides 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 nucleoside antibiotics.[12] However, only one total synthesis of such a disaccharide nucleoside was accomplished by Steavens et al. in 1972.[13] Recently, we briefly reported the formal synthesis of cytosamine, in which the 2′,3′,6′-trideoxyhexopyranosyl pyrimidine nucleoside was prepared via the intramolecular-pyrimidine-delivery method established by our group for the stereoselective synthesis of β-2′-deoxynucleosides.[14,15] In this letter, we describe the total synthesis of cytosaminomycin C based on this synthetic strategy.

The synthesis commenced with the preparation of the intramolecular-glycosylation substrate as shown in Scheme 1. Commercially available tri-*O*-acetyl-D-glucal (**1**) was converted to the phenyl 2-deoxy-1-thio-D-glucoside **2** according to the literature method.[16,17] Following removal of the acetyl groups, the C4 and C6 hydroxys were protected as a *p*-methoxybenzylidene acetal and the C3 hydroxy was protected as a silyl ether, affording compound **3**. Reductive cleavage of the *p*-methoxybenzylidene acetal in **3** with DIBAL led to the 4-*O*-*p*-methoxybenzyl derivative **4**, which was treated with sodium hydride and then 2-chloro-4-methoxypyrimidine to give the intramolecular glycosylation substrate **5**.

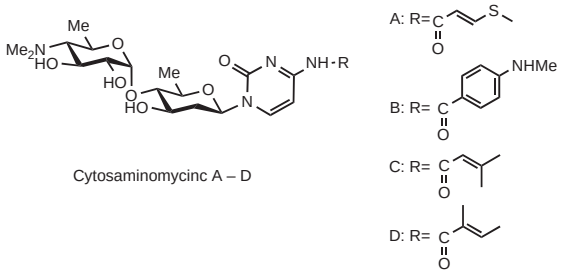
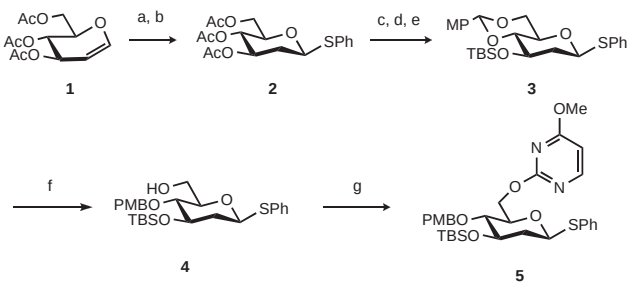


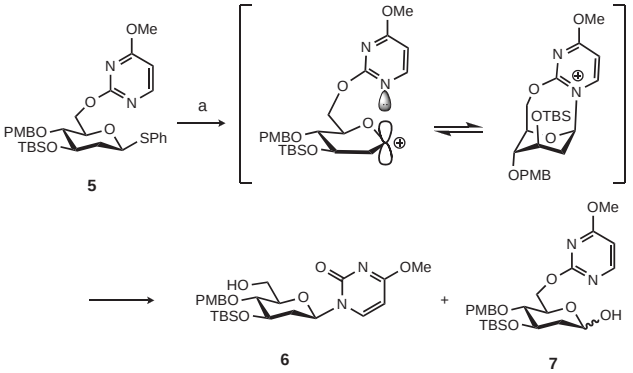
Figure 1.



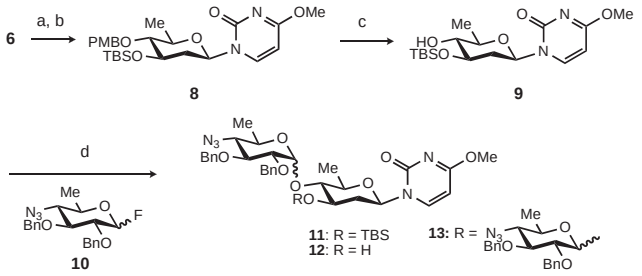
Scheme 1. *Reagents & conditions*: (a) Ph_3P–HBr, MeOH, rt, 23 h, 86%; (b) PhSH, $BF_3{\cdot}OEt_2$, 0 °C to rt, 21 h, 89%; (c) NaOMe, 0 °C, 3 h, 99%; (d) *p*-$MeOC_6H_4CH(OMe)_2$, $HBF_4{\cdot}OEt_2$, DMF, rt, 3 h, quant.; (e) *t*-$BuMe_2SiCl$, Imidazole, DMF, rt, 15 h, 91%; (f) DIBAL, CH_2Cl_2, 0 °C to rt, 9.5 h, 86%; (g) NaH, DMF, then 2-chloro-4-methoxypyrimidine, DMF, −40 to −20 °C, 26 h, 76%.

The intramolecular glycosylation was carried out using $Me_2S(SMe)BF_4$ as a promoter in acetonitrile at −20 °C (Scheme 2). The resulting α-oxocarbenium ion would be trapped by the lone pair of the pyrimidine nitrogen, leading to the cyclic pyrimidinium intermediate. The successive addition of a 1 M sodium hydroxide solution hydrolyzed this intermediate to yield the pyrimidine-migration product. After purification by silica gel chromatography, the desired 2-deoxy-β-hexopyranosyl nucleoside **6** was obtained in 74% isolated yield along with 12% of the C-1 hydrolyzed product **7**.

With the 2′-deoxy-β-nucleoside **6** in hand, our next goal



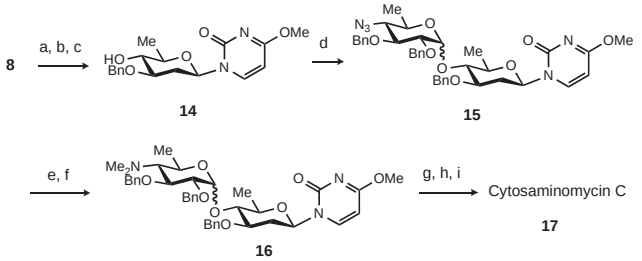
Scheme 2. *Reagents & conditions*: (a) $Me_2S(SMe)BF_4$, M.S.4A, MeCN, −20 °C, 5 h, then 1 M NaOHaq., −20 °C to 0 °C, 2 h, 74% (**6**), 12% (**7**).



Scheme 3. *Reagents & conditions*: (a) I_2, PPh_3, Py, rt, 5 h, 84%; (b) Bu_3SnH, AlBN, toluene, reflux, 14 h, 94%; (c) DDQ, CH_2Cl_2–H_2O, rt, 2 h, 79%; (d) **10**, AgOTf, $SnCl_2$, M.S.4A, Et_2O–$ClCH_2CH_2Cl$ (9:1), 0 °C to rt, 18 h, 16% (**11**, α-anomer), 39% (**12**, α-anomer), 26% (**13**, anomeric mixtures).

was the α-selective glycosylation at the 4′ position of the 2′,6′-dideoxynucleoside **9**. We planned to utilize a procedure using benzylated glycosyl fluorides by activation with a Ag^+-salt and Sn^{II} system as a promising approach.[18] The requisite acceptor **9** was prepared via the following sequence: (i) treatment of the nucleoside **6** with iodine and triphenylphosphine in pyridine, (ii) reduction of the resulting iodo group with Bu_3SnH in the presence of AIBN, and (iii) deprotection of the 4′-*O*-PMB group of **8** by treating with DDQ. The resulting nucleoside **9** was glycosylated with glycosyl fluoride **10**[15] using AgOTf and $SnCl_2$ as promoters to afford the glycosylated products (Scheme 3). However, besides the desired product **11** (16% isolated yield), the 3′ desilylated compound **12** and its glycosylated product **13** were obtained in 39% and 26% yields, respectively. This unexpected lability of the TBS group under the glycosylation conditions prompted us to change the 3′ protecting group into a more stable one prior to the glycosylation reaction (Scheme 4).

Thus, after displacement of the 3′-*O*-TBS group with the Bn group, the 4′-*O*-PMB group was removed to give the 4′ free nucleoside **14** in a good total yield. Glycosylation of **14** with the donor **10** under the same conditions described above provided the desired disaccharide nucleoside **15** in 97% yield with a moderate α-selectivity (α:β = 3.3:1). The ratio was determined by a ^{1}H NMR analysis, though the α- and β-anomers were inseparable at this stage. Subsequent reduction of the 4″-azido group in **15** was accomplished in a hydrogen atmosphere using



Scheme 4. *Reagents & conditions*: (a) Bu_4NF, THF, rt, 1 h; (b) NaH, BnBr, DMF, 0 °C, 2 h, 93% (2 steps); (c) DDQ, CH_2Cl_2–H_2O, rt, 2 h, 86%; (d) **10**, AgOTf, $SnCl_2$, M.S.4A, Et_2O–$ClCH_2CH_2Cl$ (9:1), 0 °C to rt, 18 h, 97% (α:β = 3.3:1); (e) H_2, Pd/C, MeOH, rt, 17 h; (f) HCHO, H_2, Pd/C, rt, 22 h, 82% (2 steps); (g) NH_3, MeOH, 100 °C, 16 h, 94%; (h) H_2, Pd/C, HCl aq., MeOH, rt, 70%; (i) Me_3SiCl, Py, then 3-methylcrotoyl chloride, rt, 25%.

10% Pd/C as the catalyst to give the corresponding amine, which was followed by reductive methylation by the successive addition of aqueous HCHO, affording compound **16**. The treatment of **16** with a methanol solution saturated by ammonia at 100 °C yielded the cytosine derivative. The reductive debenzylation was carried out using 10% Pd/C and HCl aq as catalysts under hydrogen. Finally, the selective acylation of the 4-amino group in the resulting free nucleoside gave the cytosaminomycin C (**17**).[19] The ^{1}H and ^{13}C NMR data of the synthetic sample were identical to those described in the literature.[1] The β-anomer was not isolated in sufficient quantity to identify.

In conclusion, we have achieved the first total synthesis of cytosaminomycin C, demonstrating the efficacy of the intramolecular glycosylation strategy for the construction of cytosamine-type disaccharide nucleoside skeletons.

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19 Compound **17**: $[\alpha]_D^{30}$ +104° (*c* 0.4, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (d, J = 6.3 Hz, 3H), 1.36 (d, J = 6.1 Hz, 3H), 1.49–1.57 (m, 1H), 1.92 (s, 3H), 2.14 (t, J = 10 Hz, 1H), 2.22 (s, 3H), 2.47 (s, 6H), 2.51–2.55 (m, 1H), 3.11 (t, J = 9.0 Hz, 1H), 3.58 (dq, J = 6.0, 9.1 Hz, 1H), 3.70 (dd, J = 3.8, 9.3 Hz, 1H), 3.78–3.81 (m, 1H), 3.93–3.97 (m, 2H), 5.04 (d, J = 3.8 Hz, 1H), 5.82–5.84 (m, 2H), 7.54 (d, J = 7.5 Hz, 1H), 7.82 (d, J = 7.5 Hz, 1H), 8.83 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.0, 19.6, 20.6, 27.8, 38.3, 41.5, 65.9, 68.8, 70.2, 70.9, 74.0, 74.4, 81.1, 88.6, 97.2, 102.3, 117.6, 143.7, 154.8, 158.8, 162.8, 165.5.

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