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Synthesis of 1,8-dioxooctahydroxanthene C-nucleosides

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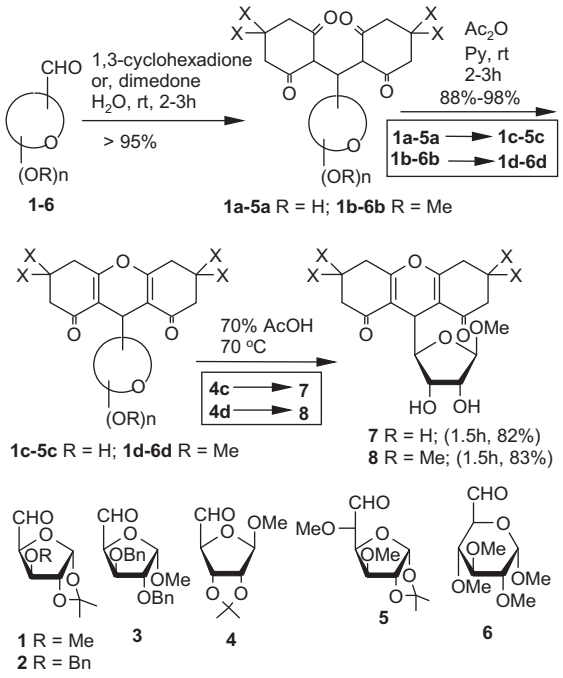
ABSTRACT

Since reactions between carbohydrates and cyclic 1,3-dicarbonyl compounds do not produce 1,8-dioxooctahydroxanthenes in general, reaction strategies have been devised to generate new 1,8-dioxooctahydroxanthene C-nucleosides by reacting sugars masked with acid-labile protecting groups and with free hydroxyl groups with 1,3-cyclohexanedione or dimedone. Some of these compounds are more cytotoxic to the cancer cells than against normal fibroblasts.

Xanthenes are an important class of organic compounds which are constituents of naturally occurring as well as synthetic derivatives and reportedly possess wide ranging pharmacological properties such as antibacterial, antiviral, and anti-inflammatory activities.[1] Xanthenediones in particular, constitute a key structural motif in a number of natural products, and have been used as versatile intermediates because of the inherent reactivity of the inbuilt pyran ring.[2a] The cancer cell cytotoxicity of 1,8-dioxooctahydroxanthenes has been documented recently.[2e] Thus, a wide range of applications in biology and material science[2g] has made 1,8-dioxooctahydroxanthenes prime synthetic candidates thereby triggering the need to develop newer synthetic routes for scaffold manipulation of this group of xanthene derivatives for accessing new chemical entities.[2] Interestingly, in spite of the well known involvement of carbohydrates in biological recognition processes[3] no attempt has been made to mimic the structures of nucleosides with 1,8-dioxooctahydroxanthene moiety replacing the nucleobases, which would have generated a new class of C-nucleosides.[4] Although the CHO group of carbohydrates and the C-1 of a glycal were reacted with 1,3-dicarbonyl compounds,[5] these reactions did not produce 1,8-dioxooctahydroxanthenes. Only scandium cation-exchanged montmorillonite mediated reactions afford 1,8-dioxooctahydroxanthenes and these reactions are one of the most inefficient synthetic procedures, requiring 2–7 days at elevated temperature and working well only with pentoses.[5,6] In any case, because of the loss of the –CHO group, in all these reported reactions the sugar residue gets converted into a polyhydroxylated chain attached to C-9 of 1,8-dioxooctahydroxanthene ring and loses its ability to provide furan/pyran type structures inherently



Scheme 1. Synthesis of protected 1,8-dioxooctahydroxanthene C-nucleosides **1**–**8**.

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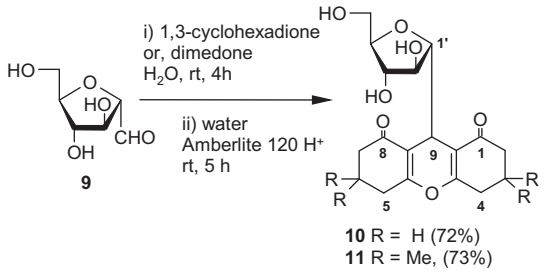

Scheme 2. One-pot synthesis of unprotected 1,8-dioxooctahydro-xanthene C-nucleosides **10** and **11**.

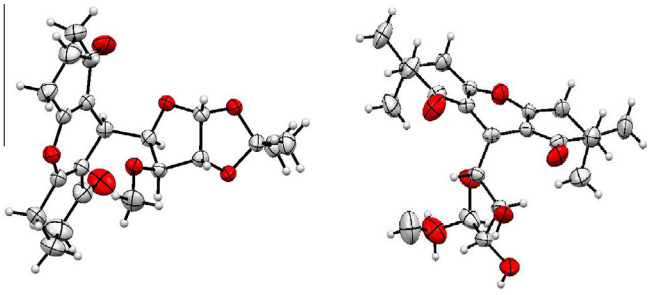

Figure 1. ORTEP of **1c** (CCDC-900335) and **11** (CCDC-900336).

associated with carbohydrates. Since these five or six-membered ring structures of carbohydrates play important roles in biological systems, we presumed that a pre-cyclized carbohydrate functionalized with a –CHO group should easily afford 1,8-dioxooctahydroxanthenes functionalized with furan or pyran moieties. Herein, we report two different strategies for the coupling of partially protected cyclic sugar aldehydes and fully unprotected cyclic sugar aldehydes with 1,3-dicarbonylcyclohexane or dimedone.

The reactions between cyclic-1,3-diketones and a variety of sugar aldehydes were carried out in water, which catalyzed the reaction by hydrogen bonding.[2b] Thus, cyclic aldehydes **1**,[7a] 2,[7b] **3**,[7c] **4**,[7d] **5**,[7e], and **6**[7e] (Scheme 1) were reacted with 1,3-cyclohexandiones or dimedone in water to get tetraketones **1a**–**5a** and **1b**–**6b**, respectively in excellent yields. Tetraketones **1a**–**5a** and **1b**–**6b** on treatment with acetic anhydride in pyridine afford 1,8-dioxooctahydroxanthene derivatives **1c**–**5c** and **1d**–**6d** in excellent yields, respectively (Scheme 1). Since acid labile groups are commonly used in carbohydrate chemistry and most of our starting carbohydrates, for example, **1**–**5** are protected with acid labile groups and/or sensitive to acidic reaction conditions, we replaced the widely used acidic reagent system[2e,2g,5] with Ac_2O/pyridine. Compounds **4c** and **4d** were deprotected by 70% AcOH in water at 70 °C within 2 h to **7** and **8**, respectively in good yields (Scheme 1). 2,5-Anhydro-D-mannose **9** (Scheme 2), available through aqueous synthetic route from glucosamine hydrochloride[7f] and structurally related to D-arabinose was utilized in a water-based strategy for the synthesis of a new class of 1,8-dioxooctahydroxanthene C-nucleosides. Thus, a colorless aqueous solution of **9** was treated with cyclic-1,3-diketones. The deep blue solution was stirred for 3–4 h at ambient temperature and activated Amberlite H^+ (IR 120) was added. The mixture was stirred for another 5 h and the deep blue solution turned dark red. After filtration, 1,8-dioxooctahydroxanthene C-nucleosides **10** and **11** were obtained as white solids during the evaporation of water at reduced pressure (Scheme 2). All spectral and analytical data correspond to the proposed structures. Identities of compounds **1c** and **11** were unambiguously confirmed from X-ray analysis of their single crystals (Fig. 1).

C-Nucleosides **10** and **11** were much better soluble in water than compounds **7** and **8**. Therefore, **10** and **11** were subjected to anticancer studies in vitro. Thus, to determine the cell viability of compounds **10** and **11**, HeLa cells (cervical cancer cell line) and L929 cells (fibroblast cell line) were cultured and treated with different concentrations (0–150 μM) of both the compounds followed by the detection of the cytotoxicity using MTT assay (Fig. 2). The percentages of viable HeLa cells relative to the untreated control cells were 63%, 61%, 58%, 49%, and 47% when cultured for 48 h with 50, 75, 100, 125, and 150 μM of compound **10**, respectively. The higher concentration of this drug was found to have a very slight effect on the growth of the normal fibroblast L929 cells. The viability of HeLa cells was reduced to 54%, 52%, 49%, 48%, and 41%, respectively in the 50, 75, 100, 125, and 150 μM of compound **11** treated cells in comparison to the untreated control cells and had no effects on the viability of L929 cells. The half maximal inhibitory concentration (IC_{50}) values for compound **10** and compound **11** after 48 h treatment were estimated to be 122.18 and 88.22 μM, respectively. As per MTT assay, **10** and **11** showed comparatively better cytotoxic effect against HeLa cells than against L929. Cytotoxic effect of compound **11** against cancer cells was found to be slightly better than that of compound **10**. Compounds **10** and **11** are not potent anticancer molecules in comparison to the known standard anticancer drugs like doxorubicin and paclitaxel.[8] However, these compounds are found to be more cytotoxic to the cancer cells than against normal fibroblast.

In conclusion, we have designed a convenient and efficient protocol for the synthesis of a hitherto unknown class of 1,8-dioxooctahydroxanthene C-nucleosides with different pentofuranosides, hexofuranosides, and hexopyranosides architechtures in high to excellent yields. The simplicity and efficiency of the methodology, ease of the product isolation, especially for compounds **10**/**11**, makes this process amenable to scaling-up. It is important to note

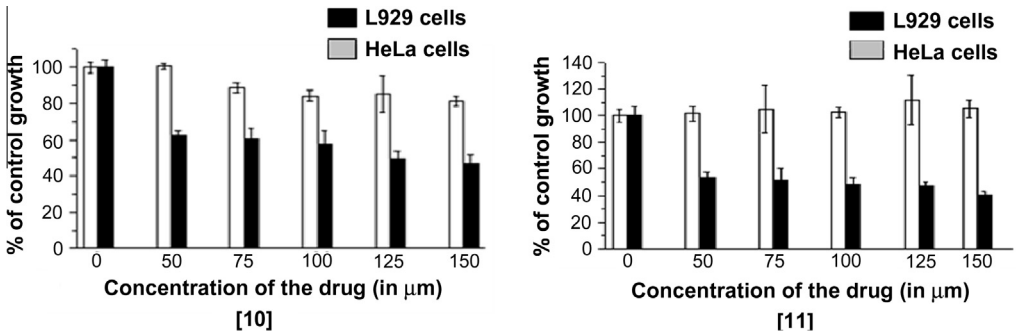

Figure 2. Cytotoxicity effects of compound **10** and **11** on HeLa and L929 cells. The cells were treated for 48 h with both the compounds at a concentration ranging from 50 to 150 μM. Cell viability was measured by MTT assay and it was expressed as the percentage of growth with respect to untreated control cells. The data were presented as the mean ± SD.

that the general nature of this strategy would also afford different C-isonucleosides depending on the availability of the appropriate cyclic sugar aldehydes. Preliminary data show that these 1,8-dioxooctahydroxanthene C-nucleosides have the potential to elicit response to biological systems. Research is currently in progress to broaden the scope of this synthesis for identifying the biological potential of these compounds.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05.067.

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