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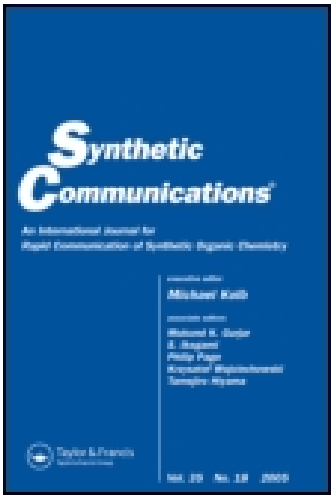


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# Cesium Carbonate–Promoted Michael-Type Addition of Thiols to Hex-1-en-3-ulose: A Practical Synthesis of 2-Deoxy-1-thio-α-hexopyranosid-3-ulose Template

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**Abstract:** The template 2-deoxy-1-thio-α-hexopyranosid-3-ulose was synthesized in quantitative yield and high diastereoselectivity by 1,4-addition of aryl and alkyl thiols to hex-1-en-3-ulose promoted by cesium carbonate in THF.

**Keywords:** cesium carbonate, 2-deoxyglycosides, 2-deoxy-1-thio-α-hexopyranosid-3-ulose, hex-1-en-3-ulose, Michael-type addition, thioglycoside

## INTRODUCTION

2-Deoxyglycosides are found in natural products such as glycopeptide antibiotics, antitumor anthracyclines, and unnatural synthetic sugars.[1] Many thioglycoside precursors have claimed their popular place in carbohydrate chemistry as glycosyl donors[2] and as precursors for anomeric sulfoxides and sulfones. Anomeric sulfoxides serve the purpose of glycosyl donor in both solution and solid-phase chemistry,[3] and anomeric sulfones can be a precursor of C-glycosides via Ramberg–Backlund reactions.[4] Furthermore, thioglycosides are attractive contributors to the temporary protection of the anomeric center.[5]

Although several synthetic approaches[6] have been reported to prepare these valuable intermediates on a small scale, many methods suffer from

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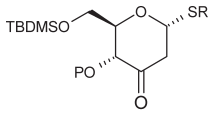


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***Figure 1.*** 2-Deoxy-1-thio-$\alpha$-D-*erythro*-hexopyranosid-3-ulose template, **5**.

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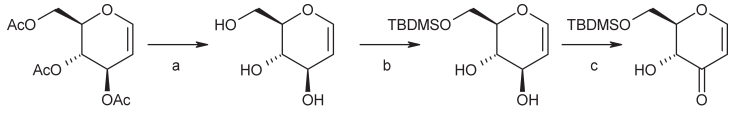
either low yields or lack of structural diversity for further synthetic utility. The utilization of the Falcks procedure[7a] for the conversion of glucals to thioglycosides involved use of triphenylphosphonium hydrobromide. This procedure generated poor anomeric mixtures (45:55) of thiosugars. Pelyvas et al.[7b] reported the use of benzyl mercaptan and a mixture of pyridine and $Et_3N$ to promote the Michael-type addition on 1,5-anhydro-2,6-didexoy hex-1-en-3-ulose. However the isolation of products was difficult. The first direct conversion of *O*-alkyl glycoside to 1-thioglycoside was reported by Hanessian and Guindon.[7c] This procedure reports low yields and only proceeds well with butane thiol. Furthermore, the expansion to large-scale preparation of the reacting species TMSSR (R = Ph, Bu, Bn) could be a challenging process.

With the current drawbacks of existing procedures and not having the flexibility of operating on a large scale, we explored a practical entry to a unique 2-deoxy-1-thio-$\alpha$-D-*erythro*-hexopyranosid-3-ulose template, **5** (Fig. 1) that would have built-in differentiation at C-1, 3, 4, and 6. This template would allow access to more versatile 2-deoxyglycoside precursors that can be used as glycosyl donors to prepare a wider range of therapeutically novel carbohydrate molecules.

## RESULTS AND DISCUSSION

As shown in Scheme 1, starting from commercially available tri-*O*-acetyl-D-glucal, **4a** was obtained in 97% overall yield using literature procedures.[7e,8a–c] The use of $MnO_2$ was reported[8d] for the oxidation of **3** but we opted to use $BaMnO_4$ because the workup called for a simple filtration through Celite® and the material recovered was used without further purification. We have successfully prepared a few hundred grams of this starting material using $BaMnO_4$. After considerable experimentation,




1 2 3 4a

***Scheme 1.*** Synthesis of **4a**. Reagents and conditions: (a) catalytic $NaOCH_3$/MeOH, 25°C; (b) TBDMSCl, Py, −10°C, 16 h; (c) $BaMnO_4$, DCM, 12 h.

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***Table 1.*** Reagents and conditions, yields and diastereoselectivities for thiol addition to **4** (Scheme 2) to obtain products **5**

| Entry | Hexenulose | Base (eq) | RSH | Solvent | °C | Time | Yield (%)[a] | Diastereoselectivity ratio $\alpha/\beta$[b] |
|---|---|---|---|---|---|---|---|---|
| 1 | **4a** | $Li_2CO_3$ (3) | BnSH | 1,4 dioxane | 25 | 24 h | NR | — |
| 2 | **4a** | $K_2CO_3$ (2) | BnSH | 1,4 dioxane | 25 | 36 h | 45[c] | 70/30 |
| 3 | **4a** | $Na_2CO_3$ (3) | BnSH | 1,4 dioxane | 25 | 24 h | NR | — |
| 4 | **4a** | $CaCO_3$ (3) | BnSH | 1,4 dioxane | 25 | 24 h | NR | — |
| 5 | **4a** | $BaCO_3$ (3) | BnSH | 1,4 dioxane | 25 | 24 h | NR | — |
| 6 | **4a** | $Cs_2CO_3$ (2) | BnSH | 1,4 dioxane | 25 | 1 h | 85 | 78/22 |
| 7 | **4a** | $Cs_2CO_3$ (2) | PhSH | 1,4 dioxane | 25 | 2 h | 70[c] | 70/30 |
| 8 | **4a** | $Et_3N$ (0.8) | BnSH | Pyridine | 25 | 8 h | 80 | 75/25 |
| 9 | **4a** | $Cs_2CO_3$ (2) | BnSH | DMF | 25 | 18 h | 70 | 80/20 |
| 10 | **4a** | $Cs_2CO_3$ (2) | BnSH | ACN | 25 | 1.5 h | 60 | 55/45 |
| 11 | **4a** | $Cs_2CO_3$ (2) | PhSH | ACN | 25 | 18 h | NR | — |
| 12 | **4a** | $Cs_2CO_3$ (1) | BnSH | THF | 0 | 15 min | 97 | 100/0 |
| 13 | **4a** | $Cs_2CO_3$ (1) | EtSH | THF | 0 | 10 min | 97 | 100/0 |
| 14 | **4a** | $Cs_2CO_3$ (1) | *n*-PrSH | THF | 0 | 10 min | 98 | 100/0 |
| 15 | **4a** | $Cs_2CO_3$ (1) | BnSH | THF | 0 | 20 min | 97 | 100/0 |
| 16 | **4a** | $Cs_2CO_3$ (1) | $C_6H_{11}SH$ | THF | 0 | 10 min | 99 | 84/16 |
| 17 | **4a** | $Cs_2CO_3$ (1) | PhSH | THF | 0 | 35 min | 98 | 60/40 |
| 18 | **4b** | $Cs_2CO_3$ (1) | BnSH | THF | 0 | 25 min | 98 | 100/0 |
| 19 | **4b** | $Cs_2CO_3$ (1) | EtSH | THF | 0 | 15 min | 96 | 100/0 |
| 20 | **4b** | $Cs_2CO_3$ (1) | PhSH | THF | 0 | 25 min | 98 | 100/0 |
| 21 | **4b** | $Cs_2CO_3$ (1) | *n*-PrSH | THF | 0 | 15 min | 97 | 100/0 |
| 22 | **4c** | $Cs_2CO_3$ (1) | $C_6H_{11}SH$ | THF | 0 | 15 min | 98 | 99/1 |

(*continued*)

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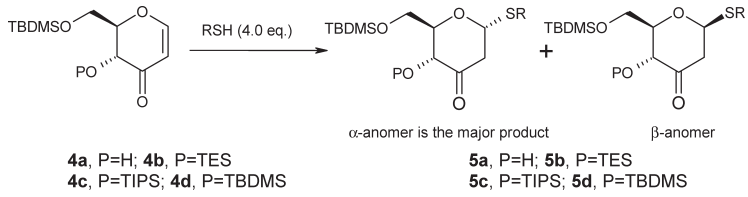
***Table 1.*** Continued

| Entry | Hexenulose | Base (eq) | RSH | Solvent | °C | Time | Yield (%)[a] | Diastereoselectivity ratio $\alpha/\beta$[b] |
|---|---|---|---|---|---|---|---|---|
| 23 | **4c** | $Cs_2CO_3$ (1) | *n*-BuSH | THF | 0 | 10 min | 98 | 100/0 |
| 24 | **4c** | $Cs_2CO_3$ (1) | PhSH | THF | 0 | 30 min | 97 | 98/2 |
| 25 | **4c** | $Cs_2CO_3$ (1) | *n*-PrSH | THF | 0 | 15 min | 97 | 97/3 |
| 26 | **4c** | $Cs_2CO_3$ (1) | *n*-BuSH | THF | 0 | 20 min | 96 | 100/0 |
| 27 | **4d** | $Cs_2CO_3$ (1) | PhSH | THF | 0 | 40 min | 97 | 99/1 |
| 28 | **4d** | $Cs_2CO_3$ (1) | *n*-BuSH | THF | 0 | 25 min | 96 | 100/0 |
| 29 | **4d** | $Cs_2CO_3$ (1) | *n*-PrSH | THF | 0 | 25 min | 98 | 100/0 |
| 30 | **4d** | $Cs_2CO_3$ (1) | EtSH | THF | 0 | 25 min | 99 | 100/0 |

[a]Isolated yield.
[b]Diastereoselectivity ratio was determined via high-field NMR spectroscopy.
[c]Yield was measured via NMR conversion. Other component identified as unreacted starting material. NR = No reaction.




***Scheme 2.*** Synthesis of 2-deoxy-1-thio-$\alpha$-D-erythro-hexopyranosid-3-ulose **5a**–**d**.

we determined that the choice of base (Table 1, entries 1–6) and the equivalents used to promote the Michael-type addition reaction with **4a** was crucial to obtain optimum yields and selectivity (Scheme 2). The results of our experiments are summarized in Table 1.

We found **4a** underwent a Michael-type addition in good yields with modest diastereoselectivity ($\alpha/\beta$ 78/22) by using excess BnSH (4 equivalents) and 2 equivalents of $Cs_2CO_3$ in 1,4-dioxane at room temperature for 1 h. We observed under these initial reaction conditions that prolonged reaction times reproduced some starting material **4a** via a $\beta$-elimination route. In addition, these side reactions were also observed during the purification process using silica-gel chromatography.

A dramatic improvement in diastereoselectivity was accomplished by reducing the amount of base to 1 equivalent, conducting the experiment at lower temperatures, and changing the solvent medium to THF. For example, the reaction performed at 0°C in THF with 1 equivalent $Cs_2CO_3$ (Table 1, entry 12) made a significant difference to both the reaction time and to the diastereoselectivity. The reaction was completed in 15 min, and only a single diastereomer was detected by NMR. We also noted that if the crude reaction product (in presence of excess thiol) is stored at $-10$°C, no $\beta$-elimination or $<5\%$ elimination was observed. To address the stability problem of **5a**, we protected the free 4-hydroxyl group as triethylsilyl (TES), triisopropylsilyl (TIPS), or *t*-butyldimethylsilyl (TBDMS) ether. As expected, conducting the same reaction with **4b**–**d**, (Table 1, entries 18, 23, 28) produced stable products **5b**–**d** with high diastereoselectivity. In most cases, the reaction times to completion were longer with aryl thiols, but all the other stability issues associated with the free OH products were resolved.

## CONCLUSION

The present method will allow for the large-scale preparation of thio-$\alpha$-2-deoxy-ulosides template (**5**). We have successfully prepared hundreds of milligrams to more than 500 g using this process. Further studies to utilize this unique 2-deoxy-1-thio-$\alpha$-D-erythro-hexopyranosid-3-ulose template are on going.

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## EXPERIMENTAL

### General

All reactions were performed under an atmosphere of dry nitrogen. Commercially available reagents were used without further purification. All products were purified by flash chromatography using silica gel 60 (79–230 mesh, Merck). The products were identified with $^{1}H$ and $^{13}C$ NMR spectral data on a Bruker 400-MHz-NMR. High-resolution mass spectrometric analysis (HRMS) was obtained with a VG Analytical ZAB 2SE mass spectrometer.

### Typical Procedure for the 1,4 Michael-type Addition

Table 1, entry 21: To a dry THF solution (10 mL) of **4b** (215 mg, 0.433 mmol) at 0°C $Cs_2CO_3$ (141 mg, 0.433 mmol) was added, followed by neat PrSH (0.203 mL, 1.73 mmol) under an $N_2$ atmosphere. The reaction was monitored by thin-layer chromatography (TLC) until disappearance of the starting material. After 15 min, the reaction was quenched with water and extracted with methylene chloride. The solvent and excess propane thiol were evaporated under reduced pressure. The crude residue was purified by flash chromatography (20% EtOAc in hexanes) to afford 256 mg of **5b** ($R{=}C_3H_7$) as a white solid in 97% yield. $^{1}H$ NMR ($CDCl_3$, $\delta$) 0.02 (s, 6H, Me), 0.47–0.58 (overlapping q, $J = 8.5$ Hz, 6H, $3 \times CH_2$ of Et), 0.78–0.87 (overlapping t, $J = 8.5$ Hz, 18H, $3 \times CH_3$ of Et and *tert*-butyl), 1.55–1.61 (m, 5H, $CH_3$ and $CH_2$ of SPr), 2.51–2.55 (m, 2H, $CH_2$ of SPr), 2.76 (d, $J = 13.1$ Hz, 1H, C2-H), 3.08 (dd, $J = 13.1$, 6.6 Hz, 1H, C2-H), 3.67 (dd, $J = 11.2$, 3.7 Hz, 1H, C6-H), 3.73 (dd, $J = 11.2$, 2.0 Hz, 1H, C6-H), 4.18 (ddd, $J = 10.1$, 3.7, 2.0 Hz, 1H, C5-H), 4.36 (d, $J = 10.1$ Hz, 1H, C4-H), 5.48 (d, $J = 6.7$ Hz, 1H, C1-H). HRMS (FAB) calcd. for $C_{21}H_{44}O_4SSi_2$: 448.8184. Found: 448.8189. Anal. calcd. for $C_{21}H_{44}O_4SSi_2$: C, 56.20; H, 9.88. Found: C, 56.31; H, 9.90.

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