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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 9195–9198

# Building carbohydrates on the dioxanone scaffold: stereoselective synthesis of D-glycero-D-manno-2-octulose

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Received 27 September 2007; revised 16 October 2007; accepted 18 October 2007
Available online 24 October 2007

**Abstract**—The title compound has been synthesized via two proline-catalyzed aldol addition reactions of 2,2-dialkyl-1,3-dioxan-5-ones: the first addition to 1,3-dithiane-2-carboxaldehyde, followed by reduction to the corresponding diol, protection of the OH groups and dithiane hydrolysis afforded a protected D-ribose that was used in the second aldol addition reaction.


Recently, higher monosaccharides (higher-carbon sugars), and carbohydrates having the backbone that is longer than the usual five or six carbon atoms, and their derivatives, have been receiving increasing attention, among other reasons, due to their interesting biological properties.[1,2] Monosaccharide derivatives having ten to twelve carbon atoms in the carbon skeleton include rare higher aldoses that occur as chiral fragments in some antibiotics, for example, hikosamine (a hemiaminal of an eleven carbon aldose), a core component of the nucleoside antibiotic Hikizimycin.[3] Other examples include lincosamine (the eight carbon carbohydrate moiety of the commercially available antibiotic Lincomycin),[4] and sialic acids[5] such as KDO ($C_8$) and KDN ($C_9$). Increasing numbers of higher monosaccharides that show interesting biological properties are being discovered in nature,[6] but overall higher sugars are still rather esoteric species. A search of the literature revealed that few higher monosaccharides had been described, especially larger than nonoses. There is a growing need for efficient synthetic methodologies to access these compounds, however, their multiple functional groups and the presence of numerous stereogenic centres make them rather challenging synthetic targets. Several synthetic approaches were developed over the years. Most of the methodologies employed abundant pentoses or hexoses as starting materials and homologation or coupling as the strategy.[7] The work of Jarosz[8a] and Dondoni[8b] deserves special mention.

During the last decade, a number of studies have appeared describing the use of 2,2-dialkyl-1,3-dioxan-5-ones as scaffolds for the synthesis of ketohexoses and other poly-oxygenated compounds and the topic has been reviewed.[9,10] Dioxanones have proven to be good substrates for reactions involving organocatalysis and several studies on the proline-catalyzed stereoselective transformations of dioxanones were reported, including the syntheses of ketohexoses and some higher sugars.[11] Below, we describe our recent observations pertaining to stereocontrolled synthesis of higher sugars from dioxanones via proline-catalyzed aldol reaction as the key step.

Our synthetic strategy is shown in Scheme 1. We visualized the synthesis of a ketooctose from two dioxanone building blocks. This, in principle, could be done either in 'one pot' or stepwise, the latter approach would necessitate using a number of different protecting groups. The successful strategy should lead to the synthesis of one enantiomer selectively, that is, the control of absolute and relative stereochemistry would be required. It should be noted that previous work on dioxanones involving enantioselective deprotonation,[12] as well as organocatalysis,[11] solved the former problem (enantioselectivity control) and we were optimistic that, in view of the extensive literature concerning diastereoselectivity control in aldol chemistry,[13] the latter problem (controlling relative stereochemistry) would also be solved. Eventually, a versatile strategy should make

*Keywords*: Higher sugars; Organocatalysis; Proline; Stereoselective aldol reaction; Dioxanone.
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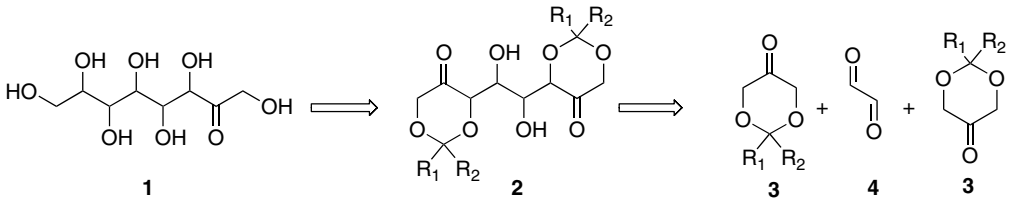
doi:10.1016/j.tetlet.2007.10.100



**Scheme 1.** Retrosynthetic plan for higher monosaccharides starting from dioxanones.

selective synthesis of several ketooctose stereoisomers possible (ideally all 32 of them). In this preliminary study, we have focused on D-glycero-D-manno-2-octulose, which is one of the natural products found in opium poppy.[14]

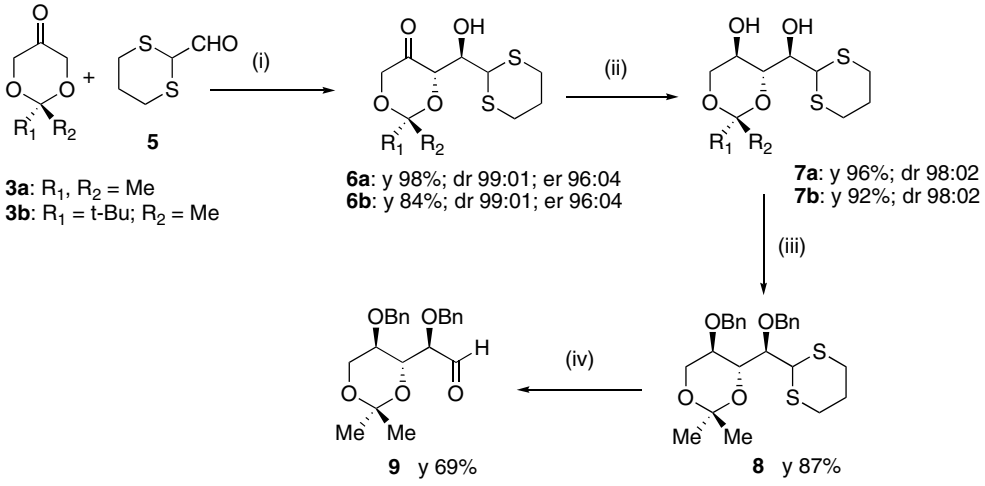
A brief experimental examination of the 'one pot' strategy yielded unpromising results. We then directed our attention to the stepwise approach.

Scheme 2 illustrates our synthesis of the chiral aldehyde reagent: a protected form of D- ribose. The precedented[11e] (*S*)-proline-catalysed aldol reaction of 2,2-dimethyl-1,3-dioxan-5-one (**3a**, dioxanone) with 1,3-dithiane-2-carbaldehyde **5** gave, in the presence of lithium chloride (a weak Lewis acid), the corresponding anti aldol product **6a**. The reaction proceeded in high yield (98%) and with high diastereo- and enantioselectivity (de 96%, ee 92%). As we have emphasized in our preceding communications,[15] the presence of LiCl was beneficial to higher selectivity. Stereoselective reduction of the aldol adduct **6a** with $NaBH(OAc)_3$ resulted in the *syn*-1,3-diol product **7a**. This interesting (note syn selectivity and not anti that might have been expected) result was in agreement with reports by both Barbas[11l] and Enders.[11e–g] The hydroxyl groups in the reduced product were protected as benzyl ethers using standard conditions giving the protected form of D-ribose, where the thioacetal group masked the aldehyde functionality. To unmask this group, compound **8** was first subjected to oxidative hydrolysis conditions using several different protocols ($HgCl_2/HgO$, $I_2/NaHCO_3$, Dess–Martin periodinane) but the reaction gave a mixture of products in each case. Fortunately, Corey's protocol[16] (NBS/$AgNO_3$ in aqueous acetonitrile) cleanly gave aldehyde **9**—a protected form of D-ribose.

To eliminate any uncertainties in stereochemical assignments at this stage we needed a crystalline derivative. Thus, we prepared compound **7b** from *tert*-butylmethyl dioxanone (**3b**) by an analogous approach (Scheme 2). Only one diastereoisomer of the aldol was detected by NMR in this case. Fortunately, the corresponding reduction product **7b** was crystalline and provided us with a crystal structure confirming the cis–*anti* stereochemistry of the aldol and the *syn* arrangement of the OH groups in the reduced aldol (Fig. 1).

With the aldehyde reagent **9** in hand, the stage was set for the key aldol reaction. We have used organocatalytic conditions and two different dioxanones as nucleophiles. The results are summarized in Table 1 (see Scheme 3).

As expected, the reaction gave two different diastereoisomeric aldols and, less expectedly, the corresponding dehydration product.[17] Interestingly, there seems to be an appreciable steric effect in the proline-mediated catalytic cycle: the reactions involving 2-*tert*-butyl-2-methyl dioxanone proceeded with higher diastereoselectivity (cf. entry 1 vs 3 and entry 2 vs 4) than the reactions with the 2,2-dimethyldioxanone. Thus, switching from $C_2$ to $C_S$-symmetrical dioxanone has substantially improved



**Scheme 2.** Synthesis of protected D-ribose. Reagents and conditions: (i) (*S*)-Proline, (30 mol%) LiCl, DMSO, 5 °C, 48 h; (ii) $NaBH(OAc)_3$, AcOH/DCM (1:5), −20 °C, 24 h; (iii) NaH, BnBr, TBAI, THF, 0 °C to rt, 6 h; (iv) NBS, $AgNO_3$, $CH_3CN/H_2O$ (4:1), 0 °C, 15 min.

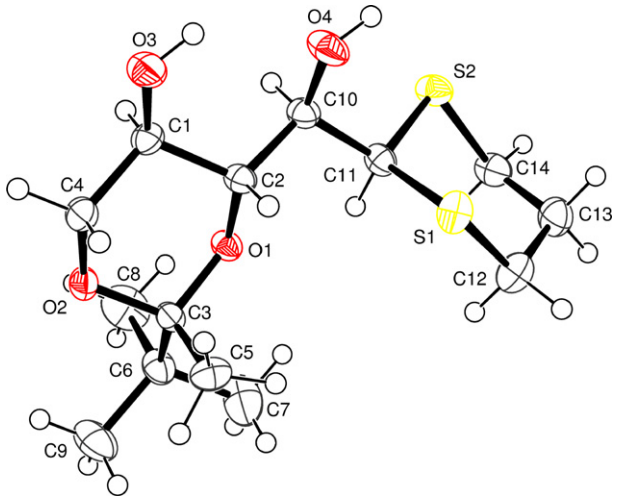



**Figure 1.** ORTEP diagram for compound **7b**.

the diastereoselectivity (de up to 92% from 34%). As reported before,[15] the addition of LiCl also improved the diastereoselectivity (cf. entries 1 and 2, and 3 with 4).

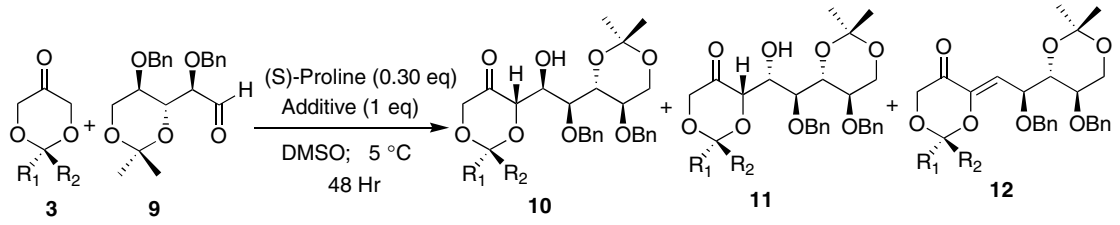
Deprotection of the aldol product **10d** was carried under acidic conditions (2 N HCl solution in THF) to provide the eight carbon monosaccharide **13**, that was isolated and characterized as the acetate derivative,[18] that is, the protected form of (+)-D-glycero-D-manno-α-oct-2-ulose **14** (25% overall yield in seven steps) as illustrated in Scheme 4.

In summary, a derivative of a naturally occurring higher sugar (+)-D-glycero-D-manno-α-oct-2-ulose **14** was synthesized in seven steps starting from commercially available dioxanone **3**, with the key stereoselective steps comprising two stereoselective aldol reactions catalyzed by proline and diastereoselective reduction of dioxanone aldol, illustrating the potential of this synthetic strategy.

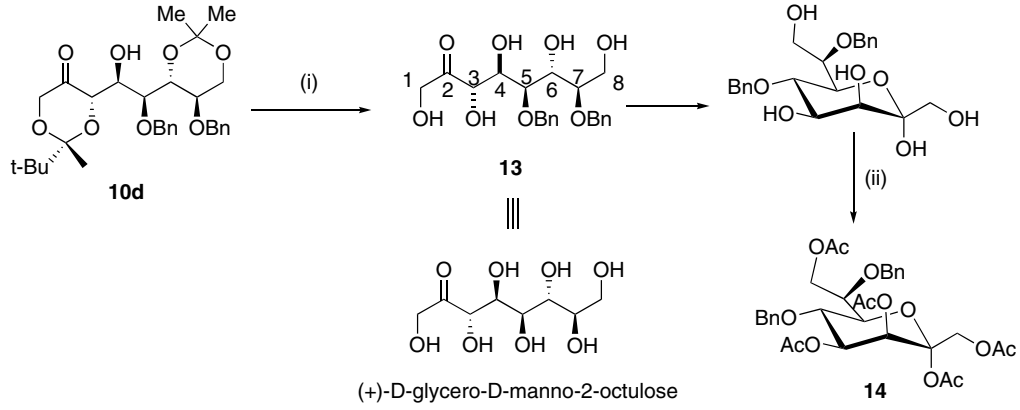
**Table 1.** Proline-catalyzed aldol addition of 1,3-dioxan-5-ones to protected D-ribose (**9**)

| Entry | Dioxanone | | Additive | Conversion[a] (%) | Yield[b] (%) | | dr[a] **10**:**11** |
|---|---|---|---|---|---|---|---|
| | $R_1$ | $R_2$ | | | **10** | **12** | |
| 1 | Me | Me | — | 92 | 42 | 22 | 2:1 |
| 2 | Me | Me | LiCl | 88 | 51 | 16 | 7:1 |
| 3 | *t*-Bu | Me | — | >98 | 56 | 14 | 9:1 |
| 4 | *t*-Bu | Me | LiCl | 94 | 69 | 8 | 16:1 |

[a] Determined by $^1$H NMR of the crude product.
[b] After column chromatography ($SiO_2$).




**Scheme 3.** Synthesis of acetonide-protected octulose (**10**).




**Scheme 4.** Synthesis of protected (+)-D-glycero-D-manno-2-octulose (**14**). Reagents and conditions: (i) 2 N HCl, THF, rt, 2 h; (ii) NaOAc, $Ac_2O$, reflux, 2 h, yield: 65%.

Further investigations to expand the scope of this methodology to the synthesis of sialic acids and other higher sugar derivatives are ongoing and will be reported in due course.

## Acknowledgements

The authors thank NSERC Canada and the University of Saskatchewan for financial support and Saskatchewan Structural Sciences Centre for help in analytical measurements. We thank Dr. J. Wilson Quail for solving the crystal structure of compound **7b**.

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17. At this stage, we could only assign stereochemistry by analogy to previously synthesized compounds and by analysis of NMR coupling constants. The absolute stereochemistry of compounds **10** and **11** is believed to be as drawn based on the following: (i) aldol addition of dioxanones to aldehydes under organocatalytic conditions is well known to give *anti* aldols with high selectivity;[11,15] (ii) aldol addition of dioxanone enolates proceeds via equatorial attack,[12] and (iii) addition of dioxanone nucleophiles to chiral aldehydes having a stereocentre at the α-carbon does not follow the Felkin-Anh model and results in the OH group at the new carbinol stereocentre being syn to the α-alkoxy group derived from the aldehyde.[12] Further details will be reported in the full paper.
18. *Compound* **14**: Sodium acetate (0.058 g, 0.70 mmol) and acetic anhydride (3 mL) were added to the crude compound **13** (25 mg, 0.06 mmol). The resulting mixture was heated to 90 °C for 2 h and the reaction was quenched with ice and with saturated $NaHCO_3$ solution. The mixture was then extracted with AcOEt ($3 \times 20$ mL) and the combined organic layers were washed with brine. The organic phase was dried over anhydrous $Na_2SO_4$ and concentrated. The crude product was purified by flash column chromatography ($SiO_2$; 30% AcOEt in hexane), which afforded the cyclized product **14** (24 mg, 65%). $[\alpha]_D^{25}$ +44.6 (*c* 1, $CHCl_3$) $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$ 7.35–7.19 (m, 10H), 5.43 (d, 1H, *J* 3.2 Hz), 5.35 (dd, 1H, $J_1$ 3.2 Hz, $J_1$ 9.9 Hz), 4.77 (dd, 2H, $J_1$ 12.1 Hz, $J_2$ 12.0 Hz), 4.65 (dd, 3H, $J_1$ 10.1 Hz, $J_2$ 11.0 Hz), 4.42 (d, 1H, *J* 12.1 Hz), 4.26 (dd, 1H, $J_1$ 8.2 Hz, $J_2$ 8.1 Hz), 4.18 (dd, 1H, $J_1$ 4.1 Hz, $J_2$ 4.0 Hz), 4.1 (t, 1H, *J* 9.9 Hz), 3.95 (dd, 1H, $J_1$ 0.92 Hz, $J_2$ 4.0 Hz), 3.82 (dd, 1H, $J_1$ 0.92 Hz, $J_2$ 9.9 Hz), 2.12 (s, 3H), 2.10 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H), 1.92 (s, 3H). $^{13}C$ NMR ($CDCl_3$, 125 MHz): $\delta$ 170.9, 170.2, 170.0, 169.6, 168.0, 138.5, 137.7, 128.7–127.9 (8 CH), 103.99, 77.96, 75.2, 74.8, 73.4, 72.5, 72.3, 67.5, 64.8, 60.6, 22.0, 21.1, 20.95, 20.87, 20.79. HRMS (CI, $NH_3$) exact mass calcd for $[M]^+$ ($C_{32}H_{38}O_{13} + NH_4^+$) required: 648.2656, found: *m/z* 648.2641. MS (CI, $NH_3$): *m/z* (%) = 648 (100) [$M+NH_4^+$], 588 (12), 571 (71), 359 (9), 240 (6), 108 (32), 91 (22), 77 (24). IR (Kubelka-Munk): 1751 (s), 1493 (w), 1451 (m) $cm^{-1}$.