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General Homologation Strategy for Synthesis of L-*glycero*- and D-*glycero*-Heptopyranoses

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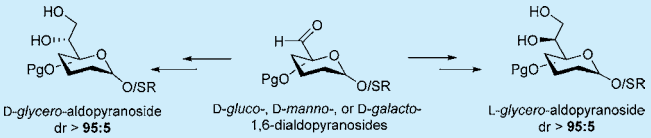
Supporting Information

ABSTRACT: A general and stereospecific homologation strategy for the synthesis of heptopyranosides is reported. The strategy employs the Wittig olefination and proline-catalyzed α-aminoxylation to achieve one carbon elongation and stereoselective hydroxylation at the C6 position, respectively. The L-*glycero*- and D-*glycero*-heptopyranosides can be obtained with nearly perfect stereoselectivity. Further study reveals the difference in the chemical shift of the C6 proton of L/D-*glycero*-heptopyranosyl diastereomers, which is found to be useful for assignment of the configuration of heptopyranosides.



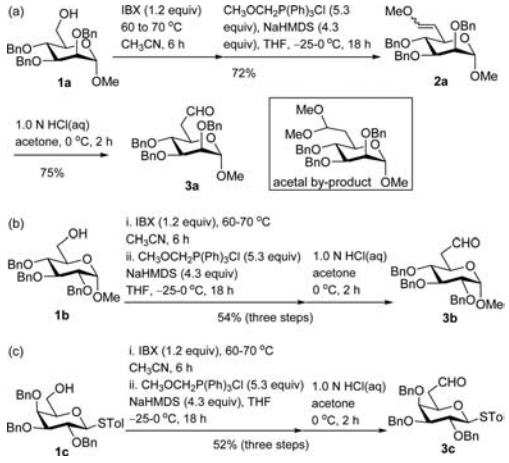
Among all monosaccharides in Nature, only a small number of hexoses and pentoses are present in sufficient quantities for commercial production; the remaining monosaccharides belong to rare sugars due to the low abundance.[1] Seven carbon sugars (L/D-heptoses) are conserved carbohydrate structural units in the majority of Gram-negative bacteria, and some are present in natural products. For example, D/L-*glycero*-D-*manno*-heptopyranoses are residues in the inner oligosaccharide core of the lipopolysaccharides (LPS) of Gram-negative bacteria.[2,3] L/D-*Glycero*-D-*gluco*- and D-*glycero*-D-*galacto*-heptopyranoses have also been found in the capsular polysaccharides of *Vibrio cholerae*,[4] *Campylobacter jejuni*,[5] and *Eubacterium saburreum*.[6]

Numerous synthetic routes have been developed for the synthesis of heptopyranosides. The most straightforward protocol is the preparation of L-*glycero*-D-*manno*-heptopyranoside via Grignard addition to a 1,6-dialdopyranoside substrate.[7] Among various Grignard reagents, (phenyldimethyl)-silylmethyl magnesium chloride offers the highest stereoselectivity.[7f−h] However, for the preparation of D-*glycero*-D-*manno*-heptopyranose, an alternative strategy is required, which invokes a Wittig olefination followed by dihydroxylation and oxidative cleavage of a diol function.[8] In addition to homologation strategies, L-*glycero*-D-*manno*-heptopyranose could be prepared from the *de novo* synthesis[9] and from D-lyxose in large scale.[10] In general, the substrate scope of the above-mentioned methods is narrow and their stereoselectivity is variable, depending heavily on the substrate structure.[7f,h,8e,f,11,12]

In this study, we report a general homologation strategy for the synthesis of L-/D-*glycero*-heptopyranosides; an extension of the method enables the synthesis of rare hexoses. Our synthetic route commences with the hexo-1,6-dialdopyranoside substrate (see Scheme S1 in Supporting Information). The substrate was first subjected to the methoxymethyl (MOM)−Wittig homologation (i) to increase the carbon chain of the substrate by one methylene unit and (ii) to introduce an enol ether function at C7.[13] Subsequent acid hydrolysis afforded hepto-1,7-dialdopyranoside for proline-catalyzed aminoxylation.[14,15] The stereochemistry of the proline-catalyzed aminoxylation is controlled by the proline catalyst; therefore, heptopyranosides with an L-*glycero*- and D-*glycero*-configuration at C6 would be obtained.

Reducing the idea to practice, a facile synthetic route to hepto-1,7-dialdopyranoside was needed. Initially, the known D-mannopyranoside **1a** was employed as a model;[16] the C6 hydroxyl of this compound was oxidized to yield the D-*manno*-1,6-dialdopyranoside (Scheme 1a). Among various oxidation methods such as Swern oxidation,[17] 2-iodoxybenzoic acid (IBX) oxidation,[18] Dess-Martin periodinane (DMP) oxidation,[19] and trichlorocyanuric acid (TCCA)−TEMPO oxidation,[20] IBX was employed for its compatibility to both of the *O*- and *S*-glycoside

Scheme 1. Synthesis of (a) D-*manno*-Hepto-1,7-dialdopyranoside 3a, (b) D-*gluco*-Hepto-1,7-dialdopyranoside 3b, and (c) Thio-β-D-*galacto*-hepto-1,7-dialdopyranoside 3c



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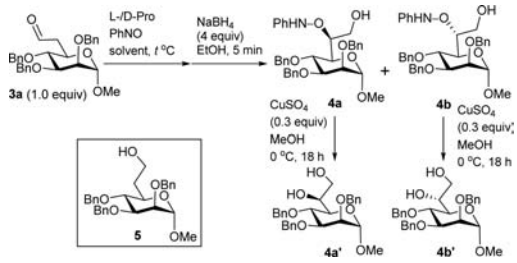
substrates. Besides, such a reagent can be prepared from 2-iodobenzoic acid.[21]

Next, the D-*manno*-1,6-dialdopyranoside obtained from IBX oxidation was treated with methoxymethyl phosphonium ylide to afford D-*manno*-hepto-6-enopyranoside **2a**. The overall yield for the oxidation and Wittig olefination was 72%. Mild acid hydrolysis of **2a** in acetone produced D-*manno*-hepto-1,7-dialdopyranoside **3a**[22a] along with a trace amount of the inseparable dimethylacetal byproduct, though such an acetal byproduct did not participate in the aminoxylation. Based on the same protocol, D-*gluco*-hepto-1,7-dialdopyranoside **3b**[22b] and 1-thio-D-*galacto*-hepto-1,7-dialdopyranoside **3c** were prepared from glucopyranoside **1b**[22c] and thiogalactopyranoside **1c**,[22d] respectively, in ca. 53% overall yield (Schemes 1b and 1c).

With the hepto-1,7-dialdopyranosides **3a**–**c** in hand, the conditions for the proline catalyzed aminoxylation were elucidated. Although this method has been used for the synthesis of small bioactive molecules,[23] the applicability to complex sugar substrates has seldom been explored.[24]

Initially, 1.0 equiv of **3a** and 20 mol % of L-proline in DMSO were treated with 1.0 equiv of nitrosobenzene (PhNO) at 25 °C (Table 1, entry 1). The reaction progress was estimated based

Table 1. Proline-Catalyzed α-Aminoxylation of 3a with PhNO



entry	solvent	L or D mol %[a]	PhNO (equiv)	t (°C), time (h)	yield (%)[b]	dr of 4a:4b[c]
1	DMSO	L, 20	1.0	25, 0.5	**4a**′, 45	>95:5
2	DMF	L, 20	1.0	25, 0.5	**4a**′, 40	>95:5
3	DMF	L, 20	1.0	0, 6.0	**4a**′, 45	>95:5
4	DMF	L, 50	1.0	0, 5.0	**4a**′, 60	>95:5
5	DMF	L, 20	1.5	0, 6.0	**4a**′, 62	>95:5
6	DMF, DMSO	L, 20	1.5	0, 6.0	**4a**′, 74	>95:5
7	DMF, DMSO	D, 20	1.5	0, 6.0	**4b**′, 76	5:>95

[a]The symbols L and D refer to L-proline and D-proline, respectively. [b]The yield reported is the overall yield from **3a** to **4a**′/**4b**′ invoking (i) one-pot aminoxylation and reduction and (ii) cleavage of anilinoxy group. [c]The dr ratios were given based on HPLC analysis of the samples **4a** and **4b** (see Supporting Information).[29]

on the color of the reaction mixture. A change in color from greenish blue to yellow implicated the completion of the reaction.[14,15] Subsequent to the aminoxylation, excess $NaBH_4$ was added to reduce the product to the L-*glycero*-D-*manno*-heptopyranoside **4a** in 45% yield, along with ca. 15% of the 6-deoxy heptopyranoside byproduct **5**.[25]

To confirm the identity of **4a**, the N–O bond of the C6 anilinoxy group was cleaved in the presence of copper sulfate ($CuSO_4$) to give the known 2,3,4-tri-*O*-benzyl-L-*glycero*-D-*manno*-heptopyranoside **4a**′.[26] The optical rotation of **4a**′ $[\alpha]_D^{25}$ in $CHCl_3$ was found to be +25.0, which agrees with the literature values, i.e. $[\alpha]_D^{25}$ of +23.0[26a] or +25.0.[26c] In addition, the spectroscopic data of **4a**′ were also consistent with the literature values, except for the chemical shift of the anomeric proton. The experimental chemical shift (δ) of the anomeric (H-1) proton is found at 4.68 ppm, while the literature value from Garegg is 6.91 ppm,[26b] but from Aspinall it is 4.65 ppm[26c] (see Table S1 in the Supporting Information). To confirm the assignment, the HSQC experiment was performed to reveal the correlation of the anomeric proton (at 4.68 ppm) and carbon (at 99.5 ppm).

Although the stereoselectivity (dr >95:5) of **4a**′ was excellent, the yield of the reaction was moderate (45%). This might be attributed to self-aldol condendation of **3a** and/or incomplete aminoxylation.[27] Next the aminoxylation was performed in DMF at 0 and 25 °C (Table 1, entries 2 and 3). The reaction was slower at 0 °C than at rt, but a cleaner reaction was obtained, indicating a reduction of self-aldol condensation.

In the literature, excess aldehyde or ketone is generally used to increase the yield of the aminoxylation.[15,28] This strategy was impractical in the present study due to the expensive access to the sugar substrate. Alternatively, the amount of the catalyst or the PhNO nucleophile could be increased to improve the conversion. Thus, (i) 50 mol % L-proline and 1.0 equiv of PhNO and (ii) 20 mol % L-proline and 1.5 equiv of PhNO were applied (Table 1, entries 4 and 5). Both conditions increased the yield of **4a**′ to *ca.* 60%. Considering the more economical use of the catalyst, 20 mol % of proline and 1.5 equiv of PhNO were employed.

A further increase in the reaction yield was achieved in a 1:1 DMF–DMSO mixture (Table 1, entry 6).[30] In such a solvent mixture, the proline catalyst could be further reduced to 5 and 10 mol %, though the reaction yield was slightly decreased (data not shown). With the use of 20 mol % D-proline catalyst, the same substrate **3a** was employed for the preparation of D-*glycero*-D-*manno*-heptopyranoside **4b**′ in 76% yield with excellent stereoselectivity (Table 1, entry 7).[26c]

Based on the established protocol in Table 1, we studied the substrate scope of application (Table 2). To this end, D-*gluco*-hepto-1,7-dialdopyranoside **3b**, D-*galacto*-hepto-1,7-dialdopyranoside **3c**, and orthogonally protected hepto-1,7-dialdopyranosides **6a**, **6b**, and **6c** were employed.

Subjecting D-*gluco*-hepto-1,7-dialdopyranoside **3b** to the L-proline-catalyzed aminoxylation, followed by reduction and cleavage of the C6 anilinoxy group, furnished L-*glycero*-D-*gluco*-heptopyranoside **7a** in 70% yield with an excellent dr of >95:5 (Table 2, entry 1).[7f,26c] To confirm the identity, **7a** was acetylated to give the known heptopyranoside **7a**′.[7f,31] The spectroscopic data of **7a** and **7a**′ agreed with the literature values (see Tables S3 and S4 in the SI). Other than the L-*glycero* D-*gluco*-heptopyranoside **7a**, the synthesis of D-*glycero*-D-*gluco*-heptopyranoside **7b** was performed with the D-proline-catalyzed aminoxylation and **7b** was also acetylated to **7b**′ (Table 2, entry 2).[7f,26c] In addition to *O*-glycosides **3a** and **3b**, the aminoxylation protocol above was applicable to thioglycosides such as 1-thio-D-*galacto*-hepto-1,7-dialdopyranoside **3c** (Table 2, entries 3 and 4).

Concerning the protecting group compatibility, hepto-1,7-dialdopyranosides **6a**–**c** with different protecting groups were examined. The thioheptopyranosides **6a**–**c** were subjected to the aminoxylation, reduction, and deprotection to produce the desired heptopyranosides **9a**, **9b**, **10a**, **10b**, and **11a** in 60% to 70% yield with almost perfect stereoselectivity regardless the variation of the protecting group pattern (Table 2, entries 5–9).

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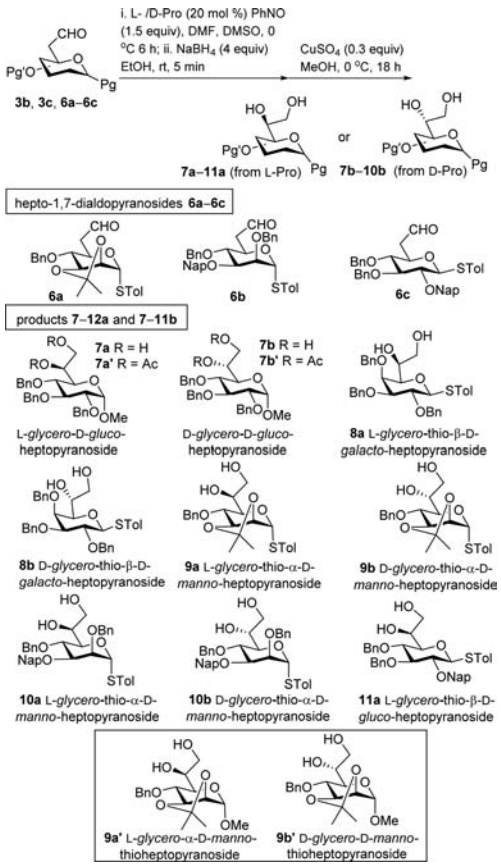
Table 2. Application of the Proline-Catalyzed Aminoxylation for the Synthesis of Heptopyranosides



entry	substrate	catalyst	product (%)[a]	dr[b]
1	**3b**	L-Proline	**7a**, 70	>95:5
2	**3b**	D-Proline	**7b**, 77	>95:5
3	**3c**	L-Proline	**8a**, 68	>95:5
4	**3c**	D-Proline	**8b**, 69	>95:5
5	**6a**	L-Proline	**9a**, 62	>95:5
6	**6a**	D-Proline	**9b**, 64	>95:5
7	**6b**	L-Proline	**10a**, 72	>95:5
8	**6b**	D-Proline	**10b**, 70	>95:5
9	**6c**	L-Proline	**11a**, 72	ND[c]

[a]Isolated yields after three steps were reported. [b]The dr ratios were determined by HPLC analysis of the crude product either before or after the cleavage of the C6 anilinoxy group.[29] [c]Only **11a** was isolated from the reaction mixture, and the dr was not determined (ND) in this example.

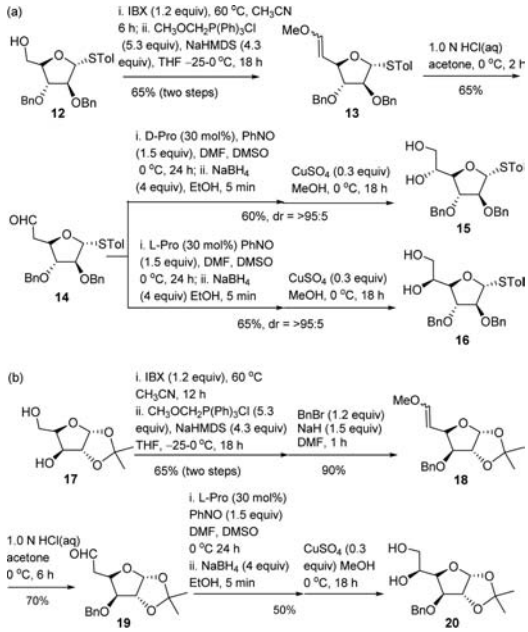
Similar to **4a**′ and **4b**′, the chemical shifts of the ^{1}H and ^{13}C NMR spectra of heptopyranosides **7a**−**11a** and **7b**−**10b** were fully assigned on the basis of 2D COSY and HSQC experiments.

As heptopyranosides **4a**′, **4b**′, **7a**, **7a**′, **7b**, and **7b**′ are known, their identities could be confirmed by comparing their spectroscopic data with the literature values (Tables S1−S6).[7f,26c,31] Closer inspection showed that the proton signal at C6 of the L-*glycero*-heptopyranosides (**4a**′, **7a**, **7a**′) was present at a more downfield position (3.98, 3.85, and 5.51 ppm) than those of the D-*glycero* diastereomers (**4b**′, **7b**, **7b**′) (3.93, 3.80, and 5.46 ppm) (Table S8, entries 1−3). Such a difference in chemical shift can also be found in L- and D-*glycero*-heptopyranosyl diastereomers reported by Zamojski[7f] and Khare.[26c] Together, the present and previous studies reveal that the difference of the chemical shift of the C6 proton of the heptopyranosyl diastereomers can be used for the assignment of the configuration. In the present study, the heptopyranosides **8a**−**10a** obtained via the L-proline aminoxylation have a more downfield C6 proton signal than those of the diastereomers **8b**−**10b** deriving from the D-proline aminoxylation (Table S8, entries 4−6). Thus, the former diastereomers **8a**−**10a** were assigned with an L-*glycero* configuration, and the latter diastereomers **8b**−**10b**, with a D-*glycero* configuration.

For validation, the known L-*glycero*-α-D-*manno*-heptopyranoside **9a**′ and unknown D-*glycero*-α-D-*manno*-heptopyranoside **9b**′ (inset in Table 2) were prepared for comparison of the spectroscopic data.[32] As expected, the chemical shift of the C6 protons of **9a**′ (at 4.00 ppm) was downfield from that of its diastereomer **9b**′ (at 3.86 ppm) (Table S8, entry 7). At this stage, it is reasonable to argue that the L-proline and D-proline catalyzed aminoxylation produces the homologation products with the L- and D-*glycero* configuration, respectively.

Rare hexoses are precious starting materials in the food and pharmaceutical industries.[33,34] Different synthetic routes have been exploited for their preparation.[35,36] Further application of the present homologation strategy was illustrated in the synthesis of several rare hexoses. The known compound D-arabinofuranoside **12** was employed as a starting substrate for the synthesis of L-galactofuranoside **15** and D-altrofuranoside **16** via a common 1,6-dialdofuranosyl intermediate **14** (Scheme 2a).[37] The aminoxylation of **14** needed a longer reaction time

Scheme 2. Synthesis of (a) D-*altro*-Thiofuranoside 15 and L-*galacto*-Thiofuranoside 16, and (b) L-Idofuranose 20



(24 h) and 30 mol % of proline, indicating a lower reactivity of the 1,6-dialdofuranosyl substrate. Note that the empirical rule for the configuration assignment of the heptopyranosides is not applicable to the furanosyl substrates **15** and **16**.[38] Building on the homologation strategy, a new synthetic route for preparation of L-idofuranose **20** from known 1,2-*O*-acetonide xylofuranose **17** was developed (Scheme 2b).[39]

In summary, a general and nearly stereospecific homologation strategy was developed for the synthesis of nonavailable heptose and hexose glycosides.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02620.

Experimental details and related references for the preparation of **3a–c**, **6a**, **6b**, **7a′**, **9a′**, **9b′**, **12**, and **17**; NMR spectra and HPLC chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

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