L-Hexoses through C–H Activation

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Synthesis of All Eight L-Glycopyranosyl Donors Using C–H Activation**

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Abstract: *The synthesis of all eight rare, but biologically important* L*-hexoses as the according thioglycosyl donors was achieved through a procedure involving the C–H activation of their corresponding 6-deoxy-*L*-hexoses. The key steps of the procedure were the silylation of the OH group at C4 followed by an intramolecular C–H activation of the methyl group in γ-position; both steps were catalyzed by iridium. The following Fleming–Tamao oxidation and acetylation gave the suitably protected* L*-hexoses. This is the first general method for the preparation of all eight* L*-hexoses as their thioglycosyl donors ready for glycosylation and the first example of an iridium-catalyzed C(sp^3)–H activation on sulfide-containing compounds.*

The rare, but biologically important L-hexoses and their corresponding 6-deoxy analogues play important roles in nature.[1] Although they are not as prevalent as their enantiomers, the D-hexoses, numerous essential biomolecules contain L-sugars. For example, L-gulose is found in the potent antitumor antibiotic bleomycin A_2 from *Streptomyces verticillus*,[2] and L-guluronic acid in alginates.[3] The extracellular polysaccharide of the anaerobic bacteria *Butyrivibrio fibrisolvens* strain CF3 contains L-altrose,[4] while L-altruronic acid has been found in the capsular polysaccharide of the Gram-positive bacteria *Aerococcus viridans* var. *homari*.[5] The capsular polysaccharide S-88 and S-130 from *Sphingomonas* both contain L-mannose and are used as gelling agents.[6] The rare L-galactose is a component of side chain A of rhamnogalacturonan-II found in pectins.[7] Littoralisone contains an L-glucoside and has been isolated from *Verbena littoralis*, which has traditionally been used in folk medicine.[8] The natural compound capuramycin contains an L-talofuranosyluronamide nucleoside,[9] and L-iduronic acid plays an important role as a component of the repeating unit of several mammalian glycosaminoglycans (GAG), that is, heparin, heparan sulfate, and dermatan sulfate.[10]

With regard to the importance of L-sugars, various methods have been explored for their synthesis.[11] One of the most investigated routes to L-sugars is the epimerization at C5 of common D-sugars, which in the case of D-glucose leads to the important L-idose.[11e] Methods of C5 epimerization include the direct nucleophilic replacement of a leaving group at C5,[12] replacement of a leaving group in constrained pentoses,[13] and the nucleophilic opening of 5,6-anhydropentoses[14a,b] and 4,5-anhydrohexoses.[14c–e] Epimerization at C5 has also been reported to proceed under Mitsunobu conditions,[15] through oxidation/stereoselective reduction,[16] base-catalyzed epimerization of uronic acids,[17] radical-induced epimerization at C5,[18] and diastereoselective hydroboration of exo- or endocyclic double bonds in unsaturated sugars.[2b,19] Homologation of sugars with shorter chains has also been reported mainly for the synthesis of L-idose.[20] Some specific L-sugars can be synthesized by the head-to-tail inversion,[21] from some common L-lactones,[22] or by (chemo)enzymatic synthesis.[23] Several de novo syntheses of L-sugars have also been developed.[24]

A major disadvantage of the above-mentioned syntheses of L-sugars is the necessity for complicated postfunctionalization in order to turn the L-sugar into a proper donor ready for glycosylation. Therefore, after the formation of the L-sugar, functionalization of the anomeric donor, for example as a thioacetal, and protection-group manipulation must be accomplished. The synthesis of already functionalized L-glycosyl donors ready for glycosylation would be highly desirable.

In view of the importance of L-hexoses in glycobiology and the practical difficulties in obtaining them from natural sources, there is an increasing need for their efficient synthesis. Recently, Hartwig and Simmons reported an iridium-catalyzed C–H activation[25–27] of methyl groups in order to introduce a carbon–silicon bond, followed by a Fleming–Tamao oxidation to give the methylene alcohol.[28] The method was applied to simple substrates and steroidal structures, but highly functionalized compounds were not used. Later, we applied the C–H activation to densely functionalized carbohydrates for the synthesis of methyl L-mannoside **5** and methyl L-galactoside **6** from their corresponding 6-deoxy L-hexoses **1** and **2** (Scheme 1).[29] The method involved an $[Ir(cod)OMe]_2$-catalyzed silylation of the OH group at C4 followed by an intramolecular C–H activation of the methyl group in γ-position, catalyzed by the same iridium catalyst in the presence of 3,4,7,8-tetramethyl-1,10-phenanthroline (Me_4Phen) as the ligand, to give oxasilolanes **3** and **4**. Fleming–Tamao oxidation of the crude oxasilolane followed by acetylation gave the L-hexoses **5** and **6** in high yields over four steps (Scheme 1).

Herein, we present the first method for the synthesis of all eight L-hexoses as the thioglycosyl donors from their corresponding 6-deoxy L-hexoses. We preferred a thiophenyl group at the anomeric position, because it is the most widely used leaving group in glycosylation chemistry and

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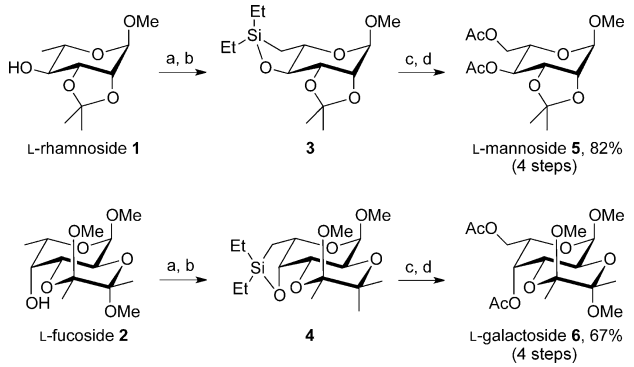


Scheme 1. Synthesis of methyl L-pyranosides from their corresponding 6-deoxy L-hexoses.[29] Reaction conditions: a) Et_2SiH_2, $[Ir(cod)OMe]_2$ (0.5 mol%), THF, RT, 13–16 h; b) $[Ir(cod)OMe]_2$ (2 mol%), Me_4Phen, norbornene, THF, 24–28 h, 120°C; c) 30% H_2O_2, $KHCO_3$, THF/MeOH (1:1), 50°C, 6 h; d) Ac_2O, DMAP, CH_2Cl_2/Et_3N, RT, 1 h. Me_4Phen = 3,4,7,8-tetramethyl-1,10-phenanthroline.

offers opportunities for both glycosylation and conversion to several other functional groups.[30] Naturally, this choice gave rise to some worries: Would the anomeric thioacetal functionality be compatible with the iridium[31]-catalyzed C–H activation and the Fleming–Tamao oxidation?[32] To the best of our knowledge, this is the first time the scope of Ir-catalyzed C(sp^3)–H activations has been expanded to include sulfides.

All eight 6-deoxy L-donors (Figure 1) were prepared from commercially available L-fucose and L-rhamnose.[33] With the substrates in hand, reaction conditions for the four-step conversion were investigated. The iridium ($[Ir(cod)OMe]_2$) catalyzed *O*-silylation with Et_2SiH_2[34] was followed by C–H activation, which proved unproblematic, when the catalyst loading was raised to 5–7 mol% along with Me_4Phen as the ligand in the presence of norbornene as H_2 scavenger (Table 1). It is worth mentioning that a slightly higher catalyst loading was necessary compared to the reactions of *O*-methyl glycosides (Scheme 1); we attributed this to the thiophilic

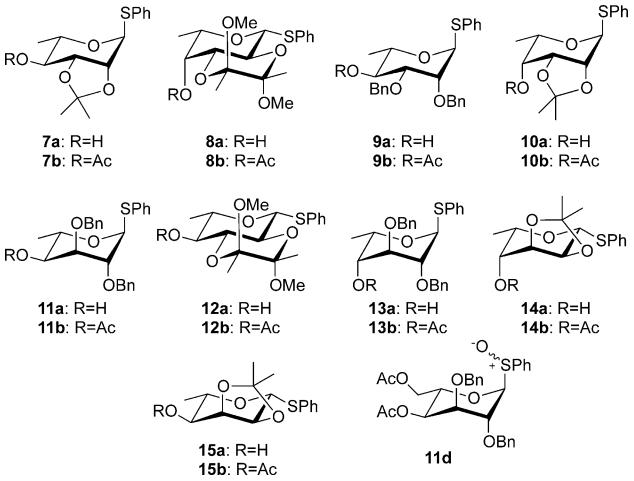
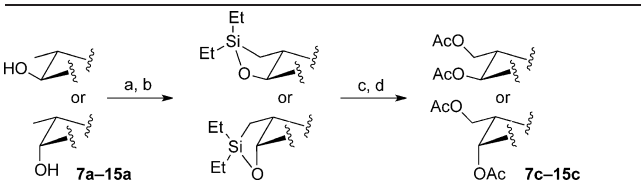
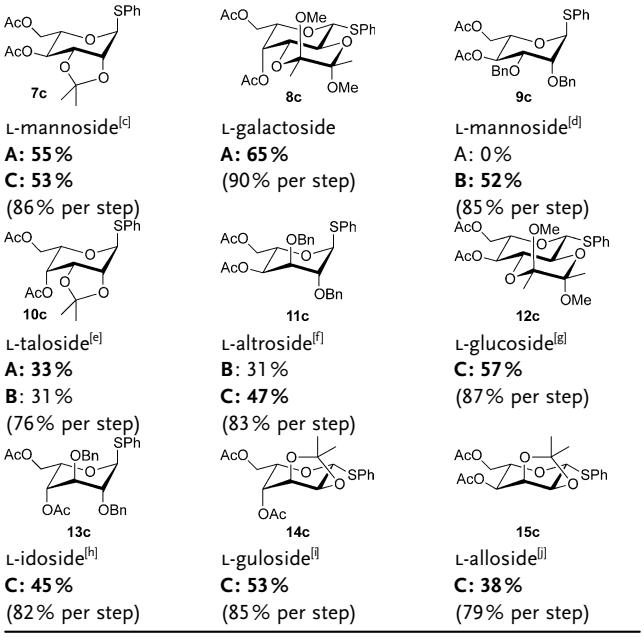


Figure 1. 6-Deoxy L-thio-glycosides used in the synthesis of the L-hexoses, the protodesilylation by-products and the sulfoxide side product **11d**.

Table 1: One-pot synthesis of L-donors via C–H activation.[a,b]





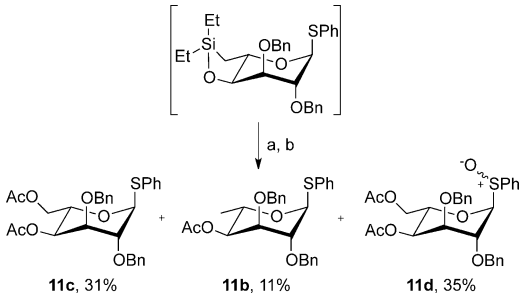
L-mannoside[c]	L-galactoside	L-mannoside[d]
A: 55%	**A: 65%**	A: 0%
C: 53%	(90% per step)	**B: 52%**
(86% per step)		(85% per step)
L-taloside[e]	L-altroside[f]	L-glucoside[g]
A: 33%	**B**: 31%	**C: 57%**
B: 31%	**C: 47%**	(87% per step)
(76% per step)	(83% per step)	
L-idoside[h]	L-guloside[i]	L-alloside[j]
C: 45%	**C: 53%**	**C: 38%**
(82% per step)	(85% per step)	(79% per step)

[a] Reaction conditions: a) Et_2SiH_2, $[Ir(cod)OMe]_2$ (0.5 mol%), THF, RT, overnight; b) $[Ir(cod)OMe]_2$ (5–7 mol%), Me_4Phen, norbornene, THF, 1–2 days, 120 °C; c) **A**: 30% H_2O_2 (10 equiv), $KHCO_3$ (2.5 equiv), THF/MeOH (1:1), 50°C, 15–18 h; **B**: UHP (30 equiv), $KHCO_3$ (5 equiv), KF (3 equiv), DMF, 50°C, 3 h; **C**: condition **B**, with K_2CO_3 as the base and 1 h reaction time; d) Ac_2O, DMAP, CH_2Cl_2/Et_3N, RT, overnight. [b] Yields (over four steps) of isolated products after column chromatography on silica gel. [c] **A**: 39% of **7b**, **C**: 37% of **7b**; large scale (Scheme 3). [d] **A**: only **9b** observed by TLC. **B**: 12% of **9b**. [e] **A**: 30% of **10b**, **B**: 16% of **10b**. [f] **B**: 11% of **11b** and 35% of the altrosyl sulfoxide **11d** (1 equiv), **C**: 23% of **11b**. [g] **C**: 35% of **12b**. [h] **C**: 35% of **13b**. [i] **C**: 36% of **14c**. [j] **C**: 45% of **15b**. cod = 1,5-cyclooctadiene.

character of iridium(I), which, to our surprise, could be overcome easily.[31] Various attempts to purify the oxasilolane intermediate failed (oxasilolanes from **7** and **9**) because of substrate decomposition. Attempts to increase the stability of these intermediates by using more bulky silane reagents were not successful.

With the conditions for the key reaction in hand, the following Fleming–Tamao oxidation[35] could be investigated. Initially, the standard conditions (i.e. $H_2O_2/KHCO_3$, conditions **A**) were applied and gave rise to the 2,3-*O*-isopropylidene-protected L-mannoside **7c** in a satisfying yield of 55% (86% per step) and the L-galactoside **8c** in an excellent yield of 65% (90% per step) over four steps. From these initial results we realized that the main by-product from the one-pot four-step synthesis was protodesilylation, which gave the acetylated starting material (**7b** and **8b**). As the standard Fleming–Tamao oxidation led to an even higher amount of the protodesilylated compound for some of the 6-deoxy

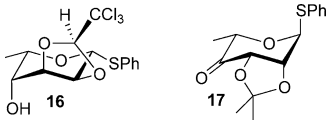
L-sugars, the reaction conditions had to be optimized.[36] The formation of the by-product of this protodesilylation was especially pronounced when 2,3-di-*O*-benzyl-protected rhamnoside **9a** was oxidized using 30% H_2O_2/$KHCO_3$, as no L-mannoside **9c** was observed. To minimize the side reaction, protic sources had to be eliminated, and the solvent was therefore changed to DMF and the solution of aqueous H_2O_2 to anhydrous urea/hydrogen peroxide complex (UHP).[37] Using this reagent system for the Fleming–Tamao oxidation together with $KHCO_3$ (conditions **B**) significantly improved the outcome of the reaction, and only 12% of the protodesilylated compound **9b** was isolated along with 52% of the desired 2,3-*O*-di-benzyl-protected L-mannoside **11c** giving a yield of 85% per step (Table 1). Improving the reaction further using other oxidation systems did not improve the yields.[38] In the synthesis of the L-taloside **10c**, no benefits were found using UHP (conditions **B**) instead of H_2O_2/$KHCO_3$ (conditions **A**), when the moderate yield was 33% over four steps (76% per step). Turning to the synthesis of L-altroside **11c**, a substantial amount of by-product was obtained using conditions **B**. After separation, the protodesilylated **11b** (11%), the L-altroside **11c** (31%), and the L-altrosyl sulfoxide **11d** (35%), derived from over-oxidation, were identified (Scheme 2).[32] Although oxidation to the L-altrosyl sulfoxide **11d** is not ideal, this compound can in fact be used in the glycosylation using Kahne's activation method mediated by triflic anhydride.[39]



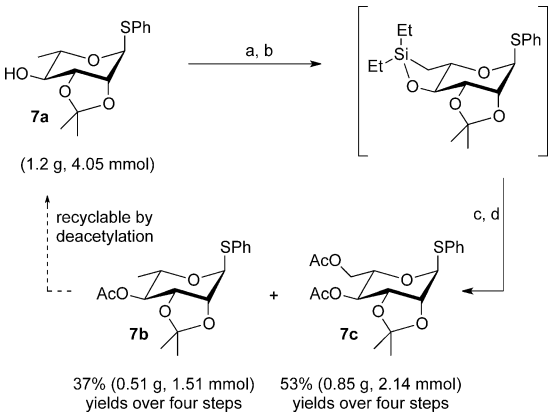
Scheme 2. Fleming–Tamao oxidation to obtain the L-altroside. Reaction conditions: a) UHP (30 equiv), KF (3 equiv), $KHCO_3$ (5 equiv), DMF, 50 °C, 3 h; b) Ac_2O, DMAP, CH_2Cl_2, Et_3N. Yields over four steps. UHP = urea/hydrogen peroxide complex.

In order to minimize the amount of the sulfoxide by-product, the reaction time was reduced to 1 h, and to remove any potential proton sources, K_2CO_3 was used instead of $KHCO_3$ (conditions **C**). Thereby, L-altroside **11c** could be synthesized in 47% yield over four steps with an average yield of 83% per step. With the optimized conditions in hand, L-glucoside **12c** (57% yield), L-idoside **13c** (45% yield), L-guloside **14c** (53% yield), and L-alloside **15c** (38% yield) were synthesized in good overall yields (Table 1) together with varying amounts of their protodesilylated analogues **12b**–**15b**, which could be recycled easily. It is worth mentioning that the procedure could be performed using standard Schlenk techniques, thereby eliminating any manipulations in the glove box.

Interestingly, the C–H activation was very selective for the methyl group at C6, leaving the methyl groups in the isopropylidene moiety and butane diacetal (BDA), and the aromatic $C(sp^2)$–H,[40] or the benzylic $C(sp^3)$–H bonds untouched.[41,42] C–H activation of trichloroethylidene-protected L-guloside **16** and 4-oxo-mannopyranoside **17** was also attempted. In case of **17**, the initial reductive silylation of the ketone should be stereoselective, giving the taloside. Unfortunately, in both cases, complicated compound mixtures were observed during the C–H activation procedure.



The four-step procedure was also applicable on a gram scale, giving the thiomannopyranoside **7c** in 53% yield over four steps (85% per step) starting with 1.2 g, thereby emphasizing the utility and scalability of the method (Scheme 3). The protodesilylated product **7b** can be recycled



Scheme 3. Gram scale synthesis of 1-thio-α-L-mannopyranoside via the four-step procedure. Reaction conditions: a) Et_2SiH_2, $[Ir(cod)OMe]_2$ (0.5 mol%), THF, RT, 17 h; b) $[Ir(cod)OMe]_2$ (7 mol%), Me_4Phen, norbornene, THF, 34 h, 120 °C; c) UHP, $KHCO_3$, KF, DMF, 50 °C, 1 h; d) Ac_2O, DMAP, CH_2Cl_2/Et_3N, RT, 15 h.

in the C–H activation procedure after deacetylation, thus limiting the waste of precious building blocks. Taking into account that the by-product can be reused in the C–H activation procedure after deacetylation, the protocol results in a yield of 84% (over four steps!) based on recovered starting material.

With all L-hexoses prepared as their thioglycosyl donors, glycosylations are possible without further modification,[30] thereby allowing the direct synthesis of various natural compounds containing L-sugars. In comparison, a known synthesis of the thio L-mannosyl donor comprised of 13 steps from an L-arabinopyranoside derivative in an overall yield of 16.8% as an anomeric mixture, thereby limiting its practical use.[43] Furthermore, an important dihydroxylation gave a mixture of two compounds, thus complicating the purification. In our method, a comparable L-mannopyranoside **9c** is

easily obtained in nine steps (only six purifications) in an overall yield of 37.5% as a single anomer. Another practical use of all eight L-hexoses as their thioglycosyl donors is their application in the study of double stereodifferentiation reactions (matched–mismatched reactions) in carbohydrate chemistry.[44] Easy access to the L-glycosyl donors can potentially confirm or reject possible matched or mismatched situations in glycosylation between the donor and the acceptor.[45] The method described herein also paves the way for an easy synthesis of all L-glycuronic acids using TEMPO/BAIB of the 4,6-unprotected sugars.[46]

In summary, we have presented a highly attractive and general method for the synthesis of the rare, but biologically important L-sugars. The method distinguishes itself from other preparation methods for L-sugars in its ability to produce the L-hexoses as their thioglycosyl donors ready for glycosylation. To our knowledge, this is the first time all eight L-hexoses have been synthesized directly as their glycosyl donors ready for glycosylation. The C–H activation is selective for the methyl group in γ-position, and can be performed on densely functionalized thioglycosides, which are the most important types of glycosyl donors in glycosylation. The usefulness of the method is also highlighted, as C–H activation is often only studied on simple substrates.

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