Sugar Synthesis

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Easy Access to L-Mannosides and L-Galactosides by Using C–H Activation of the Corresponding 6-Deoxysugars**

Tobias Gylling Frihed, Mads Heuckendorff, Christian Marcus Pedersen, and Mikael Bols**

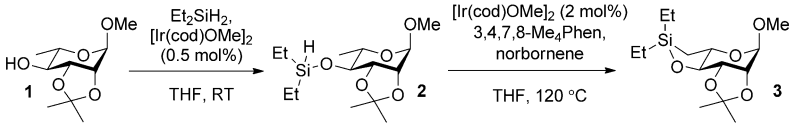
The two L-sugars L-galactose and L-mannose are found in nature, but not easily accessible. L-Galactose has been found in a marine octocoral[1] and is a constituent in some plant biopolymers. This sugar has furthermore been successfully used as mimic in sialyl Lewis^X structures.[2] L-Mannose is found in some bacteria cell-wall polysaccharides.[3] With the appearance of L-sugars in nature and their application in the development of biologically active biomimetic compounds, there is an increasing interest in their efficient synthesis. Most L-sugars are however rare in nature, but in some cases their corresponding 6-deoxysugars, such as L-fucose and L-rhamnose (the 6-deoxy analogues of L-galactose and L-mannose respectively), are more widespread and therefore easily available.

Synthesis of L-galactose and L-mannose has been known since the early days of carbohydrate chemistry and can be carried out from L-lyxose and L-arabinose respectively through chain elongation. This approach is, however, not straightforward, since diastereomeric mixtures are obtained. Other syntheses have also appeared, starting from other building blocks, but they all have the complexity and many steps in common.[4,5] De novo syntheses have been developed and are continuously improved to meet the demands for rare L-sugars.[6] A direct synthesis from the abundant 6-deoxy-sugars is therefore very desirable. Another aspect is the synthesis of β-L-rhamnosides — one of the unsolved problems in carbohydrate chemistry. Crich and Li[7] recently showed that L-mannosyl donors can solve this problem. However, the synthesis of these donors demanded more than 10 steps, which limited its practical use, and an easier access to the L-sugars from their respective 6-deoxysugars would also be an advantage here. To date this has however not been possible owing to the inherent lack of reactivity of the methyl group (C6).

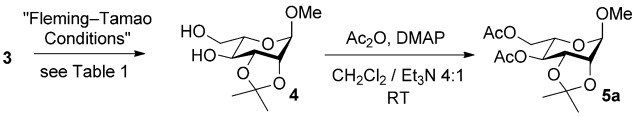
C–H activation of otherwise unreactive substrates has become a "hot topic" in chemistry with an amazing development the last few years.[8] Recently Simmons and Hartwig[9] published a very elegant iridium-catalyzed C–H activation of methyl groups to introduce a carbon–silicon bond followed by a Fleming–Tamao oxidation to give the corresponding methylene alcohol. The procedure was applied for simple substrates and for more complex steroid-based structures, but not for densely functionalized compounds, such as carbohydrates. Herein we investigate the scope of this reagent system in carbohydrate chemistry by synthesizing rare L-sugars from their more common 6-deoxy-analouges.

The substrates for the C–H activation were readily available in a few synthetic transformations from the commercially available L-rhamnose and L-fucose. The L-rhamno-model compound was synthesized by a Fischer glycosylation of L-rhamnose in methanol affording the methyl glycoside, which was directly 2,3-isopropylidinated to give the substrate **1**, having a 4-OH group ready for silylation (Scheme 1).[10]

With the first substrate in hand, the Hartwig procedure was investigated (on milli- to multiple gram scale). The 2,3-protected methyl L-rhamnoside was dissolved in THF, and subsequently the catalyst was added together with the diethyl silane under strictly inert atmosphere (Scheme 1). After complete conversion excess of the silane was removed in vacuo and additional catalyst, ligand, and norbornene (H_2 scavenger) were added together with THF. The C–H activation reaction was monitored by using GC–MS, and only a slow progress was observed when the reaction was carried out at 80 °C. Raising the temperature to 120 °C in a sealed vial significantly enhanced the reaction rate, and almost full conversion was achieved after four days. To obtain full conversion more catalyst was used (2.0 mol% in total). With the improved conditions the focus was turned to the Fleming–Tamao oxidation[11] of the cyclic silyl ether (Scheme 2). The initial experiments with the manno-derivative **3** resulted in a one-to-one mixture of two compounds,



Scheme 1. Unoptimized synthesis of cyclic silyl ether through C–H activation. Phen = 1,10-phenanthroline, cod = cycloocta-1,5-diene.



Scheme 2. Fleming–Tamao-type oxidation to give the diols.

[*] T. G. Frihed, M. Heuckendorff, Dr. C. M. Pedersen, Prof. Dr. M. Bols
Department of Chemistry, University of Copenhagen
Universitetsparken 5, DK-2100 Copenhagen Ø (Denmark)
E-mail: cmp@chem.ku.dk
bols@chem.ku.dk

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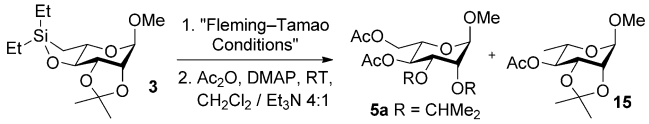
which were acetylated and purified by chromatography to give the desired L-mannoside as well as the acetylated starting L-rhamnoside (**15**, Table 1), as a result of a competing protodesilylation reaction. The modest yield in the initial reaction was found to be caused by loss of the polar diol **4** (Table 1, entries 1,2) during aqueous work-up; that is, when the water phase was concentrated and the residue was acetylated, the yield increased significantly.

Table 1: Optimizing conditions for Fleming–Tamao oxidation versus proto-desilylation in the sugar substrates.[f]

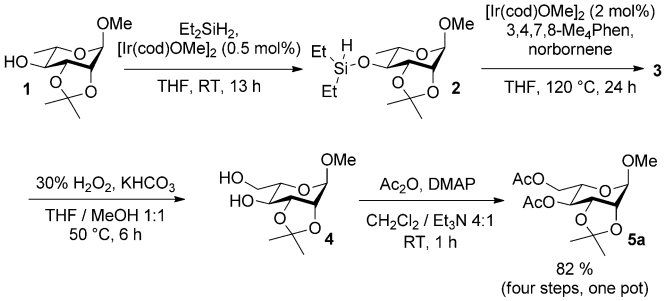


Entry	Reagents & additives	Fluoride	Solvent	*T* (*t*)	Yield of **15** [%][a]	Yield of (**5a** & **5b**) [%][b]
1[c]	30% H_2O_2, $KHCO_3$	–	THF/MeOH 1:1	50 °C (16 h)	21	20[d] (25)
2[c]	30% H_2O_2, $KHCO_3$	–	THF/MeOH 1:1	50 °C (44 h)	16	54[e] (64)
3	30% H_2O_2, $KHCO_3$	KHF_2	THF/MeOH 1:1	50 °C (44 h)	17	57[e] (69)
4	$PhMe_2COOH$, KH	TBAF	NMP	RT (22 h)	17	15[d] (18)
5	*t*BuOOH, $CsOH·H_2O$	TBAF	DMF	75 °C (8 h)	20	46[d] (58)
6	*m*-CPBA	KHF_2	DMF	RT (5 h)	18	40[d] (49)

[a] Yield of isolated product. [b] Yield of isolated **5** starting from methyl-2,3-*O*-isopropylidene-α-L-rhamnopyranoside **1** (four steps). The yield in brackets is based on recovered starting material or the protodesilylated product **1**. [c] The difference between entry 1 and 2 is the work-up procedure (see the Supporting Information). The product was also found to be in the water phase. [d] Pure **5a**. [e] Consisting of methyl-4,6-di-*O*-acetyl-2,3-*O*-isopropylidene-α-L-mannopyranoside (**5a**) and methyl-2,3,4,6-tetra-*O*-acetyl-α-L-mannopyranoside (**5b**; 4:1). [f] *m*-CPBA = *m*-chlorperbenzoic acid, TBAF = tetrabutylammonium fluoride, DMAP = 4-(dimethylamino)pyridine.

To diminish the protodesilylation side reaction, some experimentation with the reagents system was required. Addition of fluoride ions did not improve the product formation significantly (Table 1, entry 3). The use of other oxidants, such as cumene peroxide,[12] which has been found to suppress the protodesilylation side reaction, did not improve the yield of the desired L-mannoside (Table 1, entry 4). Neither *tert*-butyl peroxide[13] nor *m*-CPBA[11a] increased the yield of the L-mannoside, but shortened the reaction time. With the optimal conditions, that is, 30% H_2O_2, (KHF_2), $KHCO_3$ in THF/MeOH (Table 1, entry 2), the protected rhamnoside could be transformed into the fully protected mannoside in a four-step one-pot procedure with only one final purification to give the fully protected L-mannosides in 69% yield (based on recovered starting material, see Table 1).

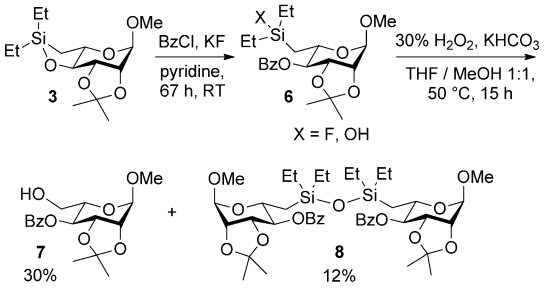
With the improved oxidation condition the reaction time in the one-pot sequence was optimized by monitoring the progress by GC–MS (Scheme 3). It was observed that the C–H activation reaction time could be reduced to 24 h when a second load of iridium catalyst and Me_4Phen were added after 18 h. Moreover, the oxidation was completed in six hours giving the diol **4**, which was acetylated in one hour to afford the desired fully protected L-mannoside **5a** in 82% yield over four steps (Scheme 3, one pot, >95% per step) together with 15% of the protodesilylated L-rhamnoside (**15**).



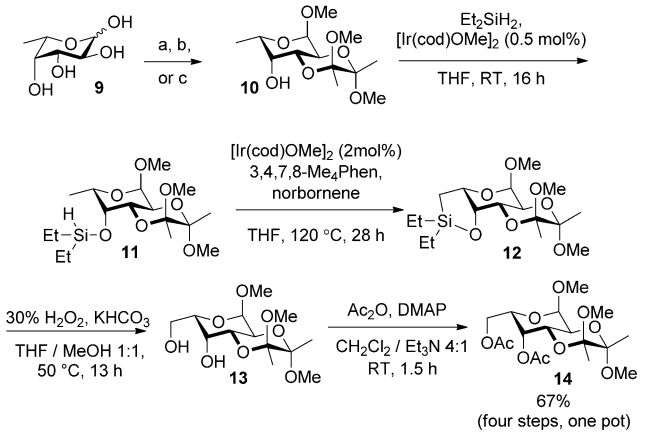
Scheme 3. Optimized one-pot sequence for the synthesis of fully protected L-mannoside **5**.

A major challenge in carbohydrate chemistry is to distinguish similar hydroxy groups by protective groups. Obviously the primary hydroxy group in the diol **4** (Scheme 3) can easily be distinguished by bulky protective groups leaving the 4-OH group free. A direct protection of the 4-OH group would be desirable, and therefore it was investigated, whether activation of the silyl group with fluoride followed by addition of an electrophile[11d,14] would lead to the protected 6-silylene compound, and whether this compound could be easily transformed into the L-mannoside having a free 6-OH group. Indeed this approach successfully afforded the 6-OH L-mannoside **7** in 30% yield again over four steps together with the dimer **8** (12%, Scheme 4).

The synthesis of L-galactosides from the corresponding L-fucoside was investigated using the model compound **10** (Scheme 5). BDA (butane-2,3-diacetal) was chosen as the protective group owing to its common use in carbohydrate chemistry and to investigate the regioselectivity of the C–H



Scheme 4. Fluoride-mediated activation of silicon followed by 4-*O*-benzoylation and Fleming–Tamao oxidation to give orthogonally protected **7**.



Scheme 5. "One-pot" synthesis of fully protected L-galactoside through C–H activation and Fleming–Tamao oxidation. a) 1. AcCl, MeOH, reflux, 19 h; 2. diacetyl, $CH(OMe)_3$, camphorsulfonic acid (CSA), MeOH, reflux, 81% (α/β 1.7:1, two steps), b) 1. MeOH, IR-120 H^+, reflux, 47% (α/β 1:0); 2. diacetyl, $CH(OMe)_3$, CSA, MeOH, reflux, 13 h, 94% (α/β 3.8:1), c) 1. MeOH, IR-120 H^+, reflux, 47% (α/β 1:0); 2. diacetyl, $CH(OMe)_3$, CSA, MeCN/MeOH (3:1), 20 h, 90% (α/β 1:0).

activation (6 methyl groups are present). Transformation of L-fucose into its 2,3-BDA-protected methyl α-L-fucoside was found to be more difficult than expected. Fischer glycosylation catalyzed by AcCl in refluxing methanol and subsequent 2,3-BDA protection[15] mediated by diacetyl, trimethyl orthoformate, and CSA in refluxing methanol[16] yielded an inseparable anomeric mixture (α/β 1.7:1) in 81% over two steps. Pure methyl α-fucoside could however easily be fractionally crystallized from an anomeric mixture of methyl L-fucoside in 47% yield[17] but gave again an inseparable anomeric mixture (α/β 3.8:1) for the BDA protection of **10** in 94%, when applying the before-mentioned conditions (Scheme 5). To avoid anomerization a milder modification of the original procedure was developed. The methyl α-L-fucoside was treated with diacetyl, trimethyl orthoformate, and $BF_3{\cdot}OEt_2$ (0.1 equiv) in MeCN/MeOH (3:1) at room temperature, giving the α-product **10** in 90% yield (Scheme 5). When **10** was submitted to the conditions optimized for the L-mannoside synthesis described above, the L-galactoside **14** was obtained in 67% yield (one pot, four steps, >90% per step) after one final purification. No protodesilylation and no C–H activation of other nearby methyl groups were observed in the L-galactoside synthesis.

In conclusion we have developed a method for easy and effective access to L-sugars from their deoxy derivatives in a few steps with only one final purification giving the desired product in outstanding yields. With four or six methyl groups in the substrates a high regioselectivity is observed, and it has furthermore been demonstrated that the reaction is independent of the relative stereochemistry (*trans* vs. *cis*) of the 4-OH and the methyl groups.

Experimental Section

Representative one-pot, one-purification procedure for the transformation of 6-deoxy sugars:

Methyl-4,6-di-*O*-acetyl-2,3-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-α-L-galactopyranoside (**14**). Methyl-2,3-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-α-L-fucopyranoside (**10**, 640 mg, 2.19 mmol) was weighed into a 25 mL flask, coevaporated twice with toluene and dried at a Schlenk line for at least 30 min. Then, the flask was transferred to an N_2-filled glove bag and $[Ir(cod)OMe]_2$ (7.4 mg, 11 μmol, 0.5 mol%) was added followed by dry and degassed THF (4 mL). Subsequently, Et_2SiH_2 (0.34 mL, 2.63 mmol, 1.2 equiv) was added (CAUTION: H_2 evolution!), and the reaction was left at room temperature under argon for 16 h, after which TLC (R_f 0.53, heptane/EtOAc 3:1) and GC–MS (*m*/*z* 363.2 (2.4% $[M-Me]^+$)) indicated complete conversion to the diethyl(hydrido)silyl ether **11**. Then, the solvent was removed by purging the mixture with nitrogen. The excess Et_2SiH_2 was removed by placing the flask under high vacuum at the Schlenk line for one hour. The crude diethyl(hydrido)silyl ether was dissolved in dry THF (3 mL) and cannulated to a dry argon-filled sealed vial containing norbornene (247 mg, 2.63 mmol, 1.2 equiv), $[Ir(cod)OMe]_2$ (10 mg, 17 μmol, 0.7 mol%), and 3,4,7,8-tetramethyl-1,10-phenanthroline (6 mg, 24 μmol, 1.1 mol%). The reaction mixture was heated at 120 °C for 28 h after which the corresponding oxasilolane **12** formed as determined by GC–MS (*m*/*z* 361.2 (1.0% $[M-Me]^+$), 345.2 (2.9% $[M-OMe]^+$)) and TLC (R_f 0.29, heptane/EtOAc 1:1). To push the reaction to completion an extra load of catalyst dissolved in THF (1 mL) was added through cannulation ($[Ir(cod)OMe]_2$, (10 mg, 17 μmol, 0.8 mol%) and ligand (6 mg, 24 μmol, 1.1 mol%)) after 22 h and stirred for additional six hours. Then, the solution was allowed to reach room temperature, transferred to a reaction flask, and concentrated. The crude reaction mixture (ca. 675 mg, 2.19 mmol) was sequentially treated with 1:1 THF/MeOH (4 mL), $KHCO_3$ (548 mg, 5.48 mmol, 2.5 equiv), and H_2O_2 (30% solution in H_2O, 2.3 mL, 21.90 mmol, 10 equiv). The resulting mixture was stirred for 13 h at 50 °C (CAUTION: CO_2 evolution!) after which TLC indicated full conversion (R_f 0.22, heptane/EtOAc 1:4) to the diol **13**. Afterwards, the reaction was coevaporated twice with toluene. The crude diol was dissolved in 4:1 CH_2Cl_2/Et_3N (10 mL), and the resulting solution was treated with DMAP (13 mg, 0.11 mmol, 0.05 equiv) and Ac_2O (2.0 mL, 21.90 mmol, 10 equiv). After being stirred at room temperature for 1.5 h the solution was coevaporated with toluene and concentrated. The crude was purified by dry column chromatography (eluent: heptane with a 1.7% gradient of EtOAc) to give the desired product **14** as a syrup in 67% yield (577 mg).

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