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Chain elongation of primary alcohols of carbohydrates

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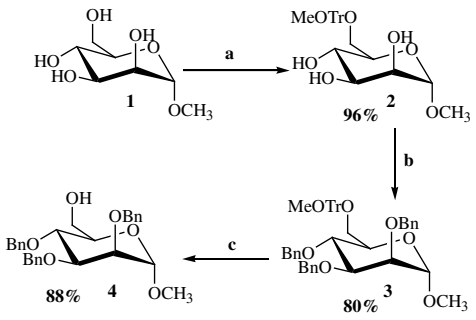
Abstract—The chain elongation of primary alcohol of saccharides (α-D-ribose, α-D-glucose, α-D-mannose) and a disaccharide (α-D-melibiose) has been achieved via a Mitsunobu reaction using bis(2,2,2-trifluoroethyl) malonate as nucleophile.

1. Introduction

The elongation of the primary alcohol of saccharides is of chemical as well as biological interest. To take one example, saccharides are natural ligands of lectins, which are receptors present on the surface of cells. The effect of homologation of a ligand-active moiety in the interaction with the lectin can lead to a better recognition between the two entities.[1] Few methods have been proposed to prepare higher homologs: substitution of a halogenated compound,[2] oxidation of the terminal hydroxymethyl group to an aldehyde followed by a Grignard[3–6] or a Wittig[7] reaction.

In contrast, an abundant literature on the Mitsunobu reaction can be found since 1967, when Mitsunobu and Yamada published their original article.[8–12] This reaction is a versatile method to condense an alcohol with an acidic compound using a redox couple, but up to now, it has not been extended to the primary alcohol of carbohydrates. Carbon–carbon bond formation by the Mitsunobu reaction is limited to nucleophiles with an acidic hydrogen. Malonates are in general not acidic enough to be used in Mitsunobu reactions. In 2002, mono- and dialkylation of bis(2,2,2-trifluoroethyl) malonate under common Mitsunobu conditions was reported by Takacs et al.[13] As part of a study to synthesize higher carbohydrate homologs, we now report the use of the Mitsunobu reaction to condense this activated malonate with the primary alcohol of a variety of carbohydrates. To achieve our goal, it was necessary to prepare carbohydrates with a free primary hydroxy group for subsequent three-carbon homologation.

Chain elongation was first achieved on α-D-mannose (Scheme 1). Methyl-α-D-mannopyranoside **1** was used to initiate the synthesis. It was first selectively protected on the primary hydroxy with a 4-methoxytrityl group to give **2**. The secondary hydroxys were then protected with benzyl groups (**2**–**3**). Compound **3** was then selectively deprotected at C-6 with ceric ammonium nitrate to afford the primary alcohol **4**. Chain elongation on compound **4** was carried out using different Mitsunobu conditions. Optimal conditions for this reaction depend upon the alcohol and nucleophile but two other parameters are also important: (a) the redox couple and (b) the solvent. Since many redox combinations have found selected use, we decided to run the reaction in toluene



Scheme 1. Reagents and conditions: (a) MeOTrCl, DMAP, pyridine; (b) BnBr, KOH, 130 °C; (c) CAN, CH_3CN–H_2O.

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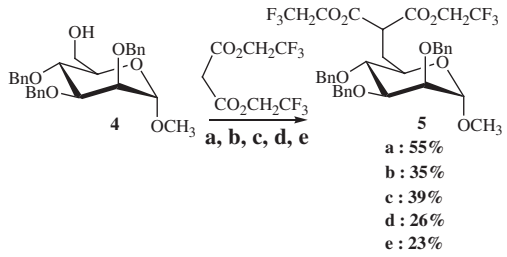


Scheme 2. Reagents and conditions: (a) ADDP/PPh_3/toluene (0.33 M); (b) same reagents (0.07 M); (c) ADDP/PPh_3/THF (0.33 M); (d) same reagents (0.07 M); (e) DIAD/PPh_3/toluene (0.33 M).

using 1,1′-(azodicarbonyl)dipiperidine and triphenylphosphine (ADDP/PPh_3) or diisopropyl azodicarboxylate and triphenylphosphine (DIAD/PPh_3) as reported in Scheme 2. The efficacy of each azodicarboxylate (2 equiv) was compared in the presence of 2 equiv of triphenylphosphine and 1.2 equiv of bis(2,2,2-trifluoroethyl) malonate in toluene. Under these conditions, it appeared that the combination ADDP/PPh_3 led to a 55% yield compared to a 23% yield obtained with the DIAD/PPh_3 couple.

Beside the redox couple, the solvent is a parameter to consider for the Mitsunobu reactions.[14] The majority of the reactions are run in tetrahydrofuran solution, but many other solvents can be used. We decided to compare two solvents: toluene and tetrahydrofuran, using two different concentrations of carbohydrate (0.07 or 0.33 M). In our case, it appeared that the higher concentration in toluene led to better results than in tetrahydrofuran (see Scheme 2).

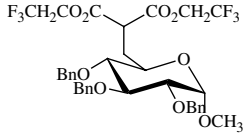
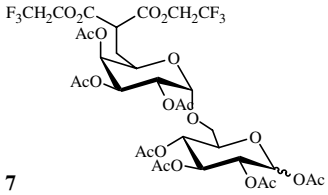
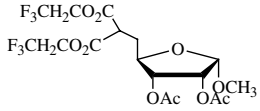
Therefore, the redox couple ADDP/PPh_3 and toluene (0.33 M) were selected to carry out the reactions on a variety of carbohydrates (Table 1).[15]

The chain elongation reaction on another hexose, α-D-glucose, was accomplished according to the results obtained with α-D-mannose. Therefore, starting from methyl-α-D-glucopyranoside the homolog **6** was obtained in four steps, following exactly the same strategy as done previously.

In order to demonstrate the generality of the method, we decided to apply this three-carbon homologation to a dissacharide and to a pentose.

In the case of the disaccharide, α-D-melibiose, it was decided to use acetyl as protecting group. It is noteworthy that acetylating the secondary hydroxys instead of benzylating them can lead to a C-4 to C-6 migration of the acetyl group. For example, in the case of mannose the migration effect decreased the yield of the Mitsunobu reaction by about 10% when acetylation was used instead of benzylation. Transesterification reactions[16] have been previously reported in the case of hexoses.[17] However, for ease of the synthesis acetylation was the method of choice for the synthesis with the disaccharide. The protection of the secondary hydroxys was run in one pot after tritylation of the primary hydroxy group. Then, the chain elongation was carried out after deprotection of the primary hydroxy, following the procedure described above to afford compound **7** (Table 1).

Table 1. Reactions of the bis(2,2,2-trifluoroethyl)malonate with different sugars following conditions: (a) reported in Scheme 2

Starting material	Product	Yield (%)
Methyl α-D-glucopyranoside	 **6**	55
α-D-Melibiose	 **7**	19
Methyl α-D-ribofuranoside	 **8**	50

In the case of pentose the C-3 to C-5 migration of the acetyl group does not occur, and, for this reason, this protecting group could be used. Compound **8** was obtained starting from methyl α-D-ribofuranoside and the chain elongation was carried out on α-D-ribofuranoside as described for the hexose (Table 1).

2. Conclusion

The homologation of primary alcohol of saccharides (pentose and hexose) and a disaccharide (α-D-melibiose) has been achieved via a Mitsunobu reaction using bis(2,2,2-trifluoroethyl)malonate as nucleophile. The ease of the synthesis make this method attractive to obtain new saccharide homologs.

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15. Experimental conditions (typical procedure): To a solution of **4** (765 mg, 1.65 mmol), bis(2,2,2-trifluoroethyl) malonate (530 mg, 1.98 mmol) and PPh_3 (866 mg, 3.3 mmol) in 5 mL of toluene were added 2 equiv of ADDP (833 mg, 3.3 mmol) over 30 min. After stirring 24 h at rt, the solvent was removed under vacuo and the crude product was purified by column chromatography on silica gel (petroleum ether, then petroleum ether/ethyl ether 85/15) to give the homolog **5** as an oil.
^{1}H NMR (400.13 MHz, $CDCl_3$) δ (ppm): 2.45 (ddd, 1H, J_{6a-5} = 10 Hz, J_{6a-6b} = −14.4 Hz, J_{6a-7} = 4.9 Hz, H_{6a}); 2.87 (ddd, 1H, J_{6b-5} = 2.6 Hz, J_{6b-6a} = −14.1 Hz, J_{6b-7} = 9 Hz, H_{6b}); 3.51 (s, 3H, OCH_3); 3.84 (td, 1H, J_{5-4} = J_{5-6a} = 9.7 Hz, J_{5-6b} = 2.6 Hz, H_5); 3.96 (t, 1H, J_{4-3} = J_{4-5} = 9.3 Hz, H_4); 4.02 (dd, 1H, J_{2-1} = 1.9 Hz, J_{2-3} = 2.9 Hz, H_2); 4.11 (dd, 1H, J_{3-2} = 3.1 Hz, J_{3-4} = 9.2 Hz, H_3); 4.11 (dd, 1H, J_{7-6a} = 5 Hz, J_{7-6b} = 9.2 Hz, H_7); 4.72 (m, 4H, H_{CH_2-CF3}); 4.84 (s, 2H, $H_{CH_2(Bn)}$); 4.87 (d, 1H, J_{1-2} = 1.7 Hz, H_1); v_0 = 4.96 (ABq, 2H, v_A = 4.93, v_B = 4,99, Δv = 24.8 Hz, J_{AB} = 12.2 Hz, $H_{CH_2(Bn)}$); v_0 = 5.06 (ABq, 2H, v_A = 4.90, v_B = 5.21, Δv = 121.8 Hz, J_{AB} = 11 Hz, $H_{CH_2(Bn)}$); 7.50–7.62 (m, 15H, H_{Ph}).
^{13}C NMR (100.62 MHz, $CDCl_3$) δ (ppm):31.5 (1C, C_6); 48.4 (1C, C_7); 55.3 (1C, OCH_3); 61.5 (q, 2C, J_{C-F} = 37.2 Hz, CH_2–CF_3); 69.5 (1C, C_5); 72.6, 73.4 and 75.7 (3C, CH_2(Bn)); 75.1 (1C, C_2); 78.7 (1C, C_4); 80.5 (1C, C_3); 99.7 (1C, C_1); 123.1 (q, 2C, J_{C-F} = 276.9 Hz, CF_3); 127.3–128.9 (15C, CH_{Ph}); 138.7, 138.8 and 138.9 (3C, CIV_{Ph}); 167.4 and 167.7 (2C, C_8).
NMR ^{19}F (188.31 MHz, $CDCl_3$) δ (ppm): −74,14 (dd, J_{F-H} = 8.5 Hz). ESI$^+$/MeOH) *m/z*: 713 $[M+Na]^+$.
ESI$^-$/MeOH) *m/z*: 737 $[M-H]^-$.
For the synthesis of bis(2,2,2-trifluoroethyl) malonate see Ref. 13.
All compounds and homologs were characterized by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and MS.
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