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An efficient synthetic route to *O*-(2-*O*-benzyl-3,4-di-*O*-acetyl-α/β-L-fucopyranosyl)-trichloroacetimidate

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ABSTRACT

An efficient synthetic route to prepare *O*-(2-*O*-benzyl-3,4-di-*O*-acetyl-α/β-L-fucopyranosyl)-trichloroacetimidate from L-fucose was developed by introducing the thiophenyl group at the anomeric center and the benzylidene functional group to protect the 3 and 4 positions. Although three approaches were considered, the best result was obtained when, after the 2-hydroxyl benzylation, both protective groups were simultaneously removed by using acetic anhydride and perchloric acid supported on silica as catalyst. Selective deacetylation of the obtained tri-*O*-acetate followed by the reaction of the resultant hemiacetal with trichloroacetonitrile and DBU afforded the trichloroacetimidate with an overall yield of 56% from the L-fucose.

1. Introduction

Flowers was the first to observe that introducing ester groups at the 3- and 4-positions of a fucosyl donor could improve the stereoselectivity compared to a perbenzylated compound [1]. Therefore, virtually all modern donors of this type incorporate ester groups at either the 4-, or 3- and 4-positions. Among these, the *O*-(2-*O*-benzyl-3,4-di-*O*-acetyl-α/β-L-fucopyranosyl)-trichloroacetimidate (Fig. 1) is an efficient fucosyl donor that provides high α stereoselectivity and good yields during fucosylation, and additionally is much more stable and easy to use with respect to the corresponding extremely reactive totally benzylated derivative.

This trichloroacetimidate has been successfully used to obtain several fucosylated protected derivatives of the *lacto*- and *neolacto*-series corresponding to important epitopes, such as Lewis^a, Lewis^x, Lewis^y [2–4] and Sialyl Lewis^x [5]. Also has been used to synthetize some human milk oligosaccharides such as 2′-fucosyllactose and 3-fucosyllactose [6]. However, despite the good qualities and proven usefulness of this donor, only one low yielding procedure for preparing this trichloroacetimidate is reported in the literature [5,6] (Scheme 1).

Despite the modifications introduced in the different reaction steps, the overall yield from L-fucose is low (20–24%), mainly because large amounts of the 2-*O*-mixed acetal (Fig. 2) are formed during the protection of the positions 3 and 4 with the isopropylidene group. As additional drawbacks, long total reaction times are required (in both cases higher than 80 h), as well as intensive chromatographic purification (6 and 5 purification steps for Variants A and B, respectively).

2. Results and discussion

To overcome all these problems, we developed an efficient procedure (including three approaches) as shown in Scheme 2.

To protect the anomeric position of L-fucose we select the thiophenyl group due to its stability and tolerance to most reaction conditions used in protecting group manipulations. At the same time, it can be easily removed without the use of expensive reagents. In our first approach the per-*O*-acetylated thioglycoside **1** was obtained with an excellent yield following the one-pot method developed by Misra et al. [7] using acetic anhydride and boron trifluoride diethyl etherate as catalyst for both, the per-*O*-acetylation of L-fucose and the further glycosylation with thiophenol. The acetyl groups of **1** were removed by the Zemplen's procedure to obtain a quantitative yield of compound **2**. To protect the positions 3 and 4 of L-fucose derivative **2**, it was decided to use the benzylidene group instead of the isopropylidene group, in order to exclude the possibility of mixed acetal formation at the 2 position. Although in the literature there are reports about mixed acetal formation

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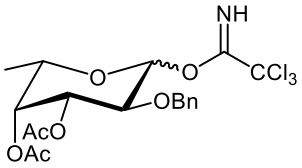


Fig. 1. Chemical structure of *O*-(2-*O*-benzyl-3,4-di-*O*-acetyl-α/β-L-fucopyranosyl)-trichloroacetimidate.

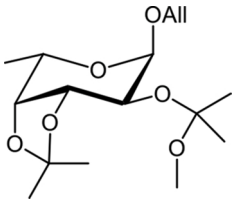


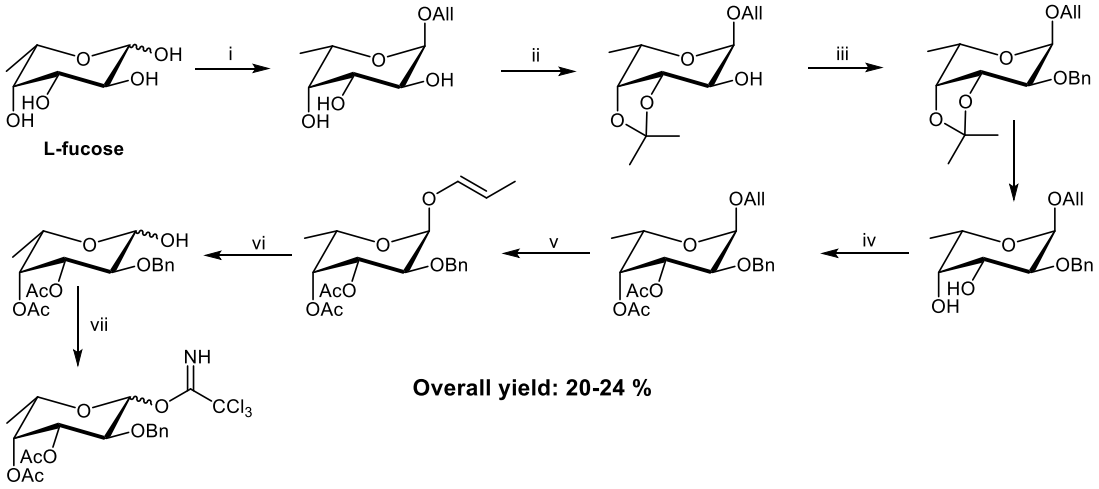
Fig. 2. Chemical structure of the 2-*O*-mixed acetal formed.

during the introduction of the benzylidene group with benzaldehyde dimethylacetal in acid media, this side reaction only occurs when is performed under reduced pressure but not under atmospheric conditions [8]. Thus, **2** was treated with benzaldehyde dimethylacetal in the presence of *p*-toluenesulfonic acid as catalyst in *N*,*N*-dimethyl-formamide to obtain the benzylidene derivative **3** as a mixture of *endo* and *exo* isomers. Since the benzylidene protective group must further be removed, both isomers were collected together during chromatographic purification and the mixture used in the next step. The benzylation of the **3** free 2-hydroxyl group was performed with benzyl bromide and sodium hydride in *N*,*N*-dimethyl-formamide to obtain compound **4** also as a mixture of the *endo* and *exo* isomers. For the same reason explained before, both isomers were collected together during chromatographic purification and the mixture used in the next step. The benzylidene group of **4** was removed in the usual way by treatment with aqueous acetic acid at 80 °C to obtain the diol **5** in a 90% yield after chromatographic purification. The acetylation of the **5** free hydroxyls with acetic anhydride/pyridine afforded the 3,4-di-*O*-acetate **6** in a quantitative yield. To cleave the anomeric thiophenyl group two methods were explored: (a) the use of *N*-bromosuccinimide in wet acetone [9,10] and (b) the treatment with *N*-iodosuccinimide/trifluoroacetic acid in a dichloromethane/water mixture [11]. Although in both cases the hemiacetal **8** was successfully obtained, a better yield was achieved when the *N*-bromosuccinimide in wet acetone technique was used (92%) as compared with the *N*-iodosuccinimide/trifluoroacetic acid method (71%). As a consequence, the former procedure was selected to obtain the compound **8**. The final step was the synthesis of the trichloroacetimidate **9** by reacting **8** with trichloroacetonitrile in the presence of 1,8-diazabicyclo [5.4.0] undec-7-ene as catalyst and dichloromethane as the solvent at room temperature. Under these conditions **9** was obtained as a α/β (9:1) mixture in 89% yield.

In a second approach and to avoid the use of pyridine, it was decided to perform the acetylation of the **5** free hydroxyls with acetic anhydride/iodine. In this case, as reported in the literature for thioglycosides [12], the acetolysis of thiophenyl group of **5** took place to obtain almost exclusively the α tri-*O*-acetate **7** in 97% yield. The treatment of compound **7** with hydrazine acetate in *N*,*N*-dimethyl-formamide afforded the hemiacetal **8** also with an excellent yield (90%), which by further reaction with trichloroacetonitrile and 1,8-diazabicyclo[5.4.0]undec-7-ene (as previously described) gave the trichloroacetimidate **9**.

Although by the two ways described before the overall yield obtained from L-fucose was 50% (almost twice the yield reported and performing the same number of synthetic steps as compared with the method described in the literature), it was decided to explore the possibility to effect the simultaneous elimination of benzylidene function and acetylation of the 3 and 4 hydroxyl groups from compound **4** by using acetic anhydride and perchloric acid supported on silica gel as catalyst, following the one pot method reported by Agnihotri et al. for 4,6-benzylidene derivatives [13]. The reaction took place in only 1 h at room temperature and a clean substitution of the anomeric thiophenyl group by an acetate group occurred to afford mainly the α tri-*O*-acetate **7** (α/β relationship 77:13). This was an expected result, since it was previously described by Agnihotri et al. [14] during the per-*O*-acetylation of thioalkyl or thioaryl glycosides with acetic anhydride and perchloric acid supported on silica gel as catalyst. The compound **7** was selectively 1-*O*-deacetylated with hydrazine acetate in *N*,*N*-dimethyl-formamide as described before to obtain de hemiacetal **8**, and the trichloroacetimidate **9** was synthetized with a similar yield, but with the advantage that this approach requires one less step and a total reaction time of only 26 h as compared with the classical method reported in the literature.

However, despite the good results obtained before, this approach required the purification of 5 intermediaries and the final product by



Scheme 1. Synthetic route reported in the literature. **Variant A** [lit. 5]. Reagents and conditions: (i) AllOH, H^+, 98 °C, 8 h; (ii) acetone, TsOH, 56 °C, 4 h; (iii) BnBr, NaH, DMF, rt, 2 h; (iv) TFA 50%, CH_2Cl_2, rt, 16 h; (v) Ac_2O, Py, rt, 16 h; (vi) $(Ph_3P)_3RhCl$, DBU, EtOH/H_2O, 80 °C, 3 h; (vii) 1 N HCl, rt, 36 h; (viii) trichloroacetonitrile, DBU, CH_2Cl_2, rt, 90 min. **Variant B** [lit. 6]. Reagents and conditions: (i) AllOH, CSA, 90 °C, 2 h; (ii) 2,2-dimethoxypropane, acetone, CSA, rt, 24 h; (iii) BnBr, NaH, TBAI, THF/DMF, rt, 16 h; (iv) AcOH 70%, 45 °C, 4 h; (v) Ac_2O, Et_3N, DMAP, rt, 16 h; (vi) $[Ir(COD)(PMePh_2)_2]^+ PF_6^-$, H_2, THF, rt, 30 min; (vii) I_2, H_2O, THF, rt, 30 min; (viii) trichloroacetonitrile, DBU, CH_2Cl_2, rt, 20 h.

column chromatography. Considering this handicap, we decided to explore the possibility of reduce the number of chromatographic purification steps. Analyzing the synthetic sequence, we concluded that the *O*-acetyl deprotection of compound **1**, the introduction of benzylidene group, the benzylation of the 2-hydroxyl and the reaction with perchloric acid supported on silica gel as catalyst could be done consecutively without the necessity of purification the intermediaries **3** and **4** by column chromatography. Thus the acetyl groups of **1** were removed by the Zemplen's procedure and after the usual work-up, the obtained residue was dissolved in *N*,*N*-dimethyl-formamide followed for the addition of benzaldehyde dimethylacetal and *p*-toluene sulfonic acid at 50 °C. When the reaction is concluded, the mixture was neutralized with triethylamine, cooled in an ice bath and treated with benzyl bromide followed by sodium hydride. After the reaction is finished, methanol was added to destroy the benzyl bromide excess, the mixture was diluted with ethyl acetate and was washed several times with a saturated aqueous solution of sodium chloride to remove the *N*,*N*-dimethyl-formamide. Finally, the obtained residue after evaporation of the organic layer was treated with acetic anhydride and perchloric acid -silica gel catalyst. Following this sequence, and after chromatographic purification, the tri-*O*-acetate **7** was obtained with an 80% overall yield from **1**. Selective 1-*O*-deacetylation of **7** and treatment of the hemiacetal **8** with trichloroacetonitrile and 1,8-diazabicyclo[5.4.0]undec-7-ene provided the trichloroacetimidate **9** with a global yield of 56% (Scheme 3).

Although the yield of the trichloroacetimidate increased in only 6%, the decision of performing the steps mentioned above without purify the intermediaries allowed to eliminate two chromatographic purification steps (only four are required now) improving even more the benefits of the best developed procedure as compared with the method reported in the literature.

3. Conclusions

The introduction of thiophenyl group at the anomeric position of L-fucose together with the protection of 3 and 4 hydroxyls with benzylidene group provided a more efficient route to prepare the *O*-(2-*O*-benzyl-3,4-di-*O*-acetyl-α/β-L-fucopyranosyl)-trichloroacetimidate (**9**). The best result was obtained when the simultaneous elimination of benzylidene function and hydroxyls acetylation were performed by using the acetic anhydride and perchloric acid supported on silica gel method and when the tri-*O*-acetate **7** was obtained from compound **1** without chromatographic purification of the intermediaries. Under these conditions, the overall yield obtained from L-fucose was 56%, higher than the reported yield (20–24%) whereas one less synthetic step and less chromatographic purifications were required as compared with the classical procedure.

4. Experimental

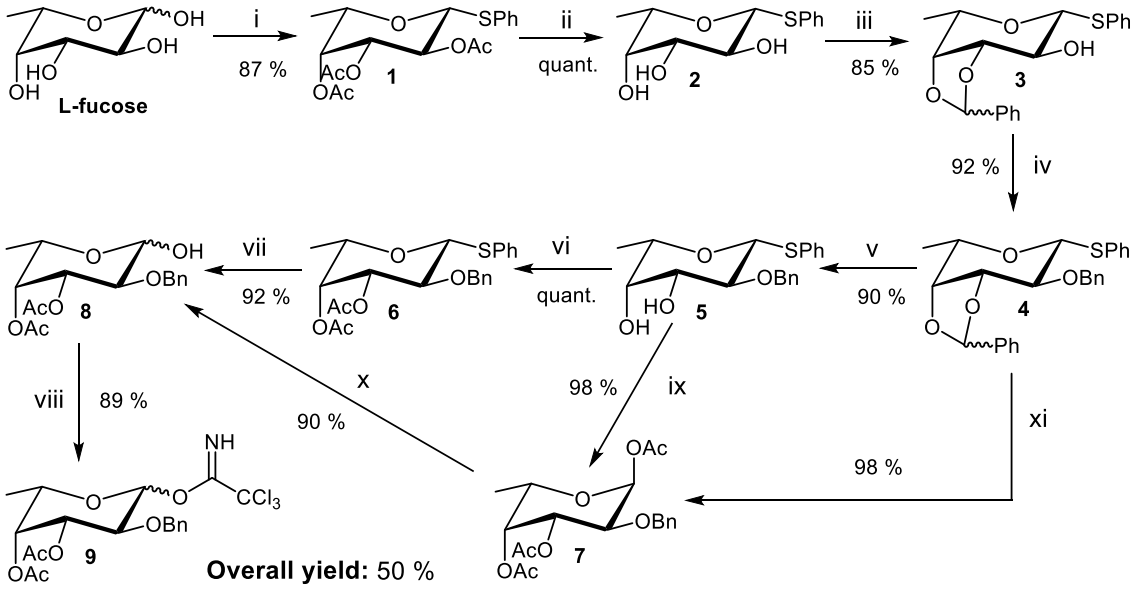
4.1. General methods

Silica gel (grade 60, 230–400 mesh) was used for column chromatography. Analytical HPTLC were performed on precoated plates of Silica gel 60, and the chromatograms were visualized by spraying the plates with 5% H_2SO_4/EtOH reagent followed by heating. Melting points (mp) were determined in a Büchi M−565 apparatus. Optical rotations were measured with an ADP 220 Bellenghan + Stanley Ltd. polarimeter at 25 °C. NMR analysis was performed on a Bruker 600 MHz Avance spectrometer and a Bruker/Avance DPX 250 MHz spectrometer.

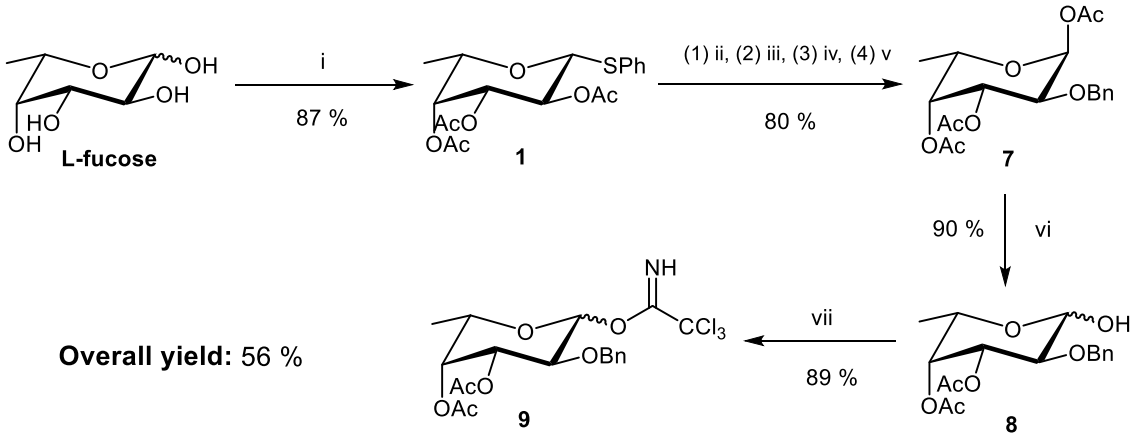
4.2. Synthetic methods

4.2.1. *Phenyl 2,3,4-tri-O-acetyl-1-thio-β-L-fucopyranoside (1)*

A suspension of L-fucose (5 g, 30.5 mmol) in Ac_2O (11.8 mL, 125 mmol) was placed in an ice bath with continuous stirring. To this cold suspension was added $BF_3{\cdot}OEt_2$ (5.8 mL, 45.8 mmol) in one portion. An exothermic reaction started immediately and the mixture was allowed to stir for 10 min. After completion of the reaction, thiophenol (4.9 mL; 47.6 mmol) was added and the reaction mixture was allowed to stir for another 4 h. The reaction was quenched by addition of aqueous $NaHCO_3$ and the mixture was extracted with CH_2Cl_2 (120 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20:1 toluene/AcOEt) to obtain **1** (Yield: 9.82 g, 87%) as a syrup: R_f: 0.30 (4:1 *n*-hexane/AcOEt); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.57–7.52 (m, 2H, aromatics), 7.34–7.31 (m, 3H, aromatics), 5.28 (dd, 1H, $J_{4,3}$ 3.4, $J_{4,5}$ 1.1 Hz, H-4), 5.24 (dd, 1H, $J_{2,1} = J_{2,3}$ 10.0 Hz, H-2),



Scheme 2. Synthetic routes developed. Reagents and conditions: (i) Ac_2O, $BF_3{\cdot}OEt_2$, rt, 10 min, then PhSH, rt, 4 h; (ii) NaOMe, MeOH, rt, 2 h; (iii) benzaldehyde dimethylacetal, *p*-TsOH, DMF, 50 °C, 1 h; (iv) BnBr, NaH, DMF, rt, 1 h; (v) aq. AcOH 80%, 80 °C, 1 h; (vi) Ac_2O, Py, rt, 6 h; (vii) NBS, acetone, H_2O, rt, 1 h; (viii) trichloroacetonitrile, DBU, CH_2Cl_2, rt, 16 h; (ix) Ac_2O, I_2, rt, 15 min; (x) hydrazine acetate, DMF, 50 °C, 30 min; (xi) Ac_2O, $HClO_4$–SiO_2, rt, 1 h.



Scheme 3. Best synthetic approach developed without chromatographic purification of the intermediaries **3** and **4**. Reagents and conditions: (i) Ac_2O, $BF_3{\cdot}OEt_2$, rt, 10 min, then PhSH, rt, 4 h; (ii) NaOMe, MeOH, rt, 2 h; (iii) benzaldehyde dimethylacetal, *p*-TsOH, DMF, 50 °C, 1 h; (iv) BnBr, NaH, DMF, rt, 1 h; (v) Ac_2O, $HClO_4$–SiO_2, rt, 1 h; (vi) hydrazine acetate, DMF, 50 °C, 30 min; (vii) trichloroacetonitrile, DBU, CH_2Cl_2, rt, 16 h.

5.07 (dd, 1H, $J_{3,2}$ 9.9, $J_{3,4}$ 3.4 Hz, H-3), 4.72 (d, 1H, $J_{1,2}$ 9.9 Hz, H-1), 3.85 (qd, 1H, $J_{5,Me}$ 6.4, $J_{5,4}$ 1.1 Hz, H-5), 2.16, 2.10, 1.99 [(s, 3H, $COCH_3$) × 3], 1.26 (d, 3H, $J_{Me,5}$ 6.4 Hz, 5-CH_3); ^{13}C NMR ($CDCl_3$, 151 MHz): δ 170.7, 170.2, 169.6, 133.0, 132.4 (2C), 129.0 (2C), 128.1, 86.6, 73.3, 72.5, 70.4, 67.5, 21.0, 20.8, 20.7, 16.5. (NMR data in agreement with reported literature [15]).

4.2.2. Phenyl 1-thio-β-L-fucopyranoside (2)

To a solution of **1** (7.6 g, 19.9 mmol) in MeOH (50 mL), a 0.3 mol/L solution of NaOMe in MeOH (18 mL) was added and the obtained mixture was stirred for 2 h at room temperature. The reaction mixture was neutralized with Amberlite IRA 120 (H^+), the resin was removed by filtration, was washed with MeOH, and the combined filtrates were evaporated to dryness under reduced pressure to obtain **2** (Yield: 5.1 g, quantitative) as a white solid: mp: 90–92 °C, lit.[15] 91–92 °C; R_f: 0.38 (15:1 CH_2Cl_2/MeOH); ^{1}H NMR (DMSO-d_6, 600 MHz): δ 7.44–7.40 (m, 2H), 7.33–7.28 (m, 2H), 7.22–7.18 (m, 1H), 5.09 (d, 1H, $J_{4\text{-}OH,4}$= 5.7 Hz, 4-OH), 4.82 (d, 1H, $J_{2\text{-}OH,2}$= 5.5 Hz, 2-OH), 4.58 (d, 1H, $J_{1,2}$ 9.3 Hz, H-1), 4.51 (d, 1H, $J_{3\text{-}OH,3}$ = 4.6 Hz, 3-OH), 3.63 (qd, 1H, $J_{5,Me}$ 6.5, $J_{5,4}$ 1.2 Hz, H-5), 3.49 (m, 1H, H-3), 3.40 (td, 1H, $J_{2,1}$ 9.2, $J_{2,3}$ 5.4 Hz, H-2), 3.36 (m, 1H, H-4), 1.12 (d, 3H, $J_{Me,5}$ 6.5 Hz); ^{13}C NMR (DMSO-d_6, 151 MHz): δ 135.4, 129.3 (2C), 128.8 (2C), 126.1, 87.3, 74.8, 73.9, 71.2, 68.9, 16.9. (NMR data in agreement with reported literature [15]).

4.2.3. Phenyl 3,4-O-benzylidene-1-thio-β-L-fucopyranoside (3)

To a solution of **2** (4.8 g, 18.7 mmol) in DMF (24 mL), benzaldehyde dimethylacetal (4.3 mL, 28.6 mmol) was added, followed by *p*-toluenesulfonic acid monohydrate (0.36 g, 1.9 mmol) and the obtained mixture was stirred at 50 °C (bath temperature) for 1 h. After completion of the reaction, the solution was neutralized with Et_3N, was diluted with AcOEt (300 mL) and was washed with saturated NaCl solution (10 × 35 mL). The organic layer was dried over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (6:1 toluene/AcOEt), to obtain **3** as a mixture of *endo* and *exo* isomers (Yield: 5.48 g, 85%). Analytical samples of the *exo* and *endo* isomers were obtained by silica gel column chromatography using the same solvent system.

***Endo* isomer:** a white solid: mp: 109–110 °C; R_f: 0.12 (4:1 *n*-hexane/AcOEt); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.61–7.55 (m, 2H, aromatics), 7.40–7.28 (m, 8H, aromatics), 5.92 (s, 1H, CHPh), 4.46 (d, 1H, $J_{1,2}$ 10.2 Hz, H-1), 4.20 (dd, 1H, $J_{3,2}$ 6.8, $J_{3,4}$ 5.8 Hz, H-3), 4.10 (dd, 1H, $J_{4,3}$ 5.9, $J_{4,5}$ 2.3 Hz, H-4), 3.97 (qd, 1H, $J_{5,Me}$ 6.6, $J_{5,4}$ 2.3 Hz, H-5), 3.55 (ddd, 1H, $J_{2,1}$ 9.7, $J_{2,3}$ 6.8, $J_{2,2\text{-}OH}$ 2.5 Hz, H-2), 2.49 (d, 1H, $J_{2\text{-}OH,2}$ 2.5 Hz, 2-OH), 1.52 (d, 3H, $J_{Me,5}$ 6.6 Hz, 5-CH_3); ^{13}C NMR ($CDCl_3$, 151 MHz): δ 137.4, 133.3 (2C), 131.6, 129.5, 129.1 (2C), 128.5 (2C), 128.3, 126.8 (2C), 104.7, 87.5, 78.9, 78.7, 72.7, 71.7, 17.1.

***Exo* isomer:** a white solid: mp: 115–116 °C; R_f: 0.42 (4:1 *n*-hexane/AcOEt). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.61–7.56 (m, 2H, aromatics), 7.47–7.42 (m, 2H, aromatics), 7.40–7.30 (m, 6H, aromatics), 6.10 (s, 1H, CHPh), 4.50 (d, 1H, $J_{1,2}$ 10.1 Hz, H-1), 4.39 (dd, 1H, $J_{3,2}$ 7.0, $J_{3,4}$ 5.3 Hz, H-3), 4.02 (dd, 1H, $J_{4,3}$ 5.3, $J_{4,5}$ 2.0 Hz, H-4), 3.86 (qd, 1H, $J_{5,Me}$ 6.6, $J_{5,4}$ 2.0 Hz, H-5), 3.73 (ddd, 1H, $J_{2,1}$ 9.8, $J_{2,3}$ 7.1, $J_{2,2\text{-}OH}$ 2.4 Hz, H-2), 2.68 (d, 1H, $J_{2\text{-}OH,2}$ 2.4 Hz, 2-OH), 1.47 (d, 3H, $J_{Me,5}$ 6.5 Hz, 5-CH_3); ^{13}C NMR ($CDCl_3$, 151 MHz): δ 138.9, 132.8 (2C), 132.2, 129.2 (2C), 129.1, 128.5 (2C), 128.2, 126.2 (2C), 103.31, 88.1, 80.1, 76.3, 73.1, 69.2, 17.2.

4.2.4. Phenyl 2-O-benzyl-3,4-O-benzylidene-1-thio-β-L-fucopyranoside (4)

To a solution of **3** (4 g, 11.6 mmol, the mixture of *endo* and *exo* isomers) in DMF (43 mL), benzyl bromide (1.76 mL, 14.8 mmol) was added, the solution was cooled to 0–5 °C, a 60% dispersion of NaH in mineral oil (0.61 g, 15.3 mmol) was then added and the mixture was stirred for 1 h at room temperature. After completion of the reaction, MeOH (4 mL) was added; the mixture was stirred for 15 min, was diluted with AcOEt (40 mL) and washed with saturated NaCl solution (10 × 15 mL). The organic layer was dried over anhydrous Na_2SO_4, the solvents were evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography (8:1 hexane/AcOEt) to obtain **4** as a mixture of *endo* and *exo* isomers (Yield: 4.64 g, 92%). Analytical samples of the *exo* and *endo* isomers were obtained by silica gel column chromatography using the same solvent system.

***Endo* isomer:** a syrup: R_f: 0.62 (6:1 *n*-hexane/AcOEt); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.58–7.54 (m, 2H, aromatics), 7.43–7.32 (m, 8H, aromatics), 7.32–7.26 (m, 5H, aromatics), 5.92 (s, 1H, CHPh), 4.73 (d, 1H, $J_{H,H'}$ 11.3 Hz, CH_2Ph), 4.65 (d, 1H, $J_{1,2}$ 9.7 Hz, H-1), 4.57 (d, 1H, $J_{H,H'}$ 11.3 Hz, CH_2Ph), 4.39 (dd, 1H, $J_{3,2} = J_{3,4}$ 6.2 Hz, H-3), 4.14 (dd, 1H, $J_{4,3}$, 6.2, $J_{4,5}$ 2.2 Hz, H-4), 3.94 (qd, 1H, $J_{5,Me}$ 6.6, $J_{5,4}$ 2.2 Hz, H-5), 3.55 (dd, 1H, $J_{2,1}$ 9.7, $J_{2,3}$ 6.1 Hz, H-2), 1.50 (d, 3H, $J_{Me,5}$ 6.6 Hz, 5-CH_3); ^{13}C NMR ($CDCl_3$, 151 MHz): δ 138.0, 137.4, 133.3, 132.7 (2C), 129.5, 128.9 (2C), 128.5 (2C), 128.4 (2C), 128.3 (2C), 127.8, 127.6, 127.1 (2C), 104.6, 86.0, 79.6, 78.9, 78.5, 73.3, 72.5, 17.0.

***Exo* isomer:** a white solid: mp: 97–99 °C; R_f: 0.80 (6:1 *n*-hexane/AcOEt); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.60–7.57 (m, 2H, aromatics), 7.47–7.44 (m, 3H, aromatics), 7.43–7.27 (m, 10H, aromatics), 6.01 (s, 1H, CHPh), 4.91 (d, 1H, $J_{H,H'}$ 11.3 Hz, CH_2Ph), 4.81 (d, 1H, $J_{H,H'}$ 11.3 Hz, CH_2Ph), 4.70 (d, 1H, $J_{1,2}$ 9.4 Hz, H-1), 4.57 (dd, 1H, $J_{3,2} = J_{3,4}$ 6.0 Hz, H-3), 4.11 (dd, 1H, $J_{4,3}$ 5.6, $J_{4,5}$ 1.9 Hz, H-4), 3.81 (qd, 1H, $J_{5,Me}$ 6.6, $J_{5,4}$ 1.9 Hz, H-5), 3.67 (dd, 1H, $J_{2,1}$ 9.4, $J_{2,3}$ 6.3 Hz, H-2), 1.44 (d, 3H, $J_{Me,5}$ 6.5 Hz, 5-CH_3); ^{13}C NMR ($CDCl_3$, 151 MHz): δ 138.8, 137.8, 133.9, 132.2 (2C), 129.4, 128.9 (2C), 128.6 (2C), 128.5 (4C), 128.0, 127.6, 126.4 (2C), 103.5, 86.3, 80.6, 76.6, 75.8, 73.6, 72.9, 17.1. (NMR data in

agreement with reported literature [16]).

4.2.5. *Phenyl 2-O-benzyl-1-thio-β-L-fucopyranoside* (5)

A suspension of **4** (4.3 g, 9.9 mmol, the mixture of *endo* and *exo* isomers) in aqueous 80% AcOH solution (88 mL) was stirred for 1 h at 80 °C (bath temperature). After completion of the reaction, the solvents were removed by evaporation under reduced pressure followed by co-evaporation with toluene and the obtained residue was purified by silica gel column chromatography (2:1 *n*-hexane/AcOEt), to obtain **5** (Yield: 3.1 g, 90%) as a white solid: mp: 106–108 °C; R_f: 0.05 (2:1 n-hexane/AcOEt); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.59–7.55 (m, 2H, aromatics), 7.42–7.26 (m, 8H, aromatics), 4.95 (d, 1H, $J_{H,H'}$ 11.0 Hz, CH_2Ph), 4.69 (d, 1H, $J_{H,H'}$ 11.0 Hz, CH_2Ph), 4.61 (d, 1H, $J_{1,2}$ 9.7 Hz, H-1), 3.72 (m, 1H, H-3), 3.65 (1H, m, H-4), 3.61 (qd, 1H, $J_{5,Me}$ 6.4, $J_{5,4}$ 1.0 Hz, H-5), 3.55 (dd, 1H, $J_{2,1} = J_{2,3}$ 9.3 Hz, H-2), 2.64 (d, 1H, $J_{4\text{-}OH,4}$ 5.3 Hz, 4-OH), 2.31 (d, 1H, $J_{3\text{-}OH,3}$ 5.1 Hz, 3-OH), 1.35 (d, 3H, $J_{Me,5}$ 6.5 Hz, 5-CH_3); ^{13}C NMR ($CDCl_3$, 151 MHz): δ 138.2, 134.1, 131.8 (2C), 129.1 (2C), 128.7 (2C), 128.4 (2C), 128.2, 127.6, 87.5, 78.2, 75.4, 75.3, 74.6, 71.8, 16.8. (NMR data in agreement with reported literature [16]).

4.2.6. *Phenyl 2-O-benzyl-3,4-di-O-acetyl-1-thio-β-L-fucopyranoside (6)*

To a solution of **5** (3 g, 8.7 mmol) in pyridine (11 mL), Ac_2O (11 mL, 116 mmol) was added and the mixture was stirred for 6 h at room temperature. After completion of the reaction, the obtained solution was cooled to 0–5 °C, MeOH (4 mL) was added, the mixture was stirred for 15 min and the solvents were evaporated under reduced pressure followed by co-evaporation with toluene to obtain **6** (Yield: 2.74 g, quantitative) as a white solid: mp: 123–124 °C; lit.[17] 124 °C; R_f: 0.47 (4:1 n-hexane/AcOEt); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.62–7.58 (m, 2H, aromatics), 7.36–7.26 (m, 8H, aromatics), 5.26 (dd, 1H, $J_{4,3}$ 3.3, $J_{4,5}$ 1.0 Hz, H-4), 5.03 (dd, 1H, $J_{3,2}$ 9.6, $J_{3,4}$ 3.3 Hz, H-3), 4.85 (d, 1H, $J_{H,H'}$ 10.9 Hz, CH_2Ph), 4.71 (d, 1H, $J_{1,2}$ 9.7 Hz, H-1), 4.58 (d, 1H, $J_{H,H'}$ 10.9 Hz, CH_2Ph), 3.80 (qd, 1H, $J_{5,Me}$ 6.4, $J_{5,4}$ 1.0 Hz, H-5), 3.73 (dd, 1H, $J_{2,1} = J_{2,3}$ 9.7 Hz, H-2), 2.15, 1.93 [(s, 3H, $COCH_3$) × 2], 1.23 (d, 3H, $J_{Me,5}$ 6.5 Hz, 5-CH_3); ^{13}C NMR ($CDCl_3$, 151 MHz): δ 170.6, 170.1, 138.1, 133.7, 132.1 (2C), 129.0 (2C), 128.5 (2C), 128.0 (2C), 127.9, 127.7, 87.8, 75.5, 75.2, 74.7, 73.0, 71.0, 20.8 (2C), 16.7. (NMR data in agreement with reported literature [17]).

4.2.7. *2-O-benzyl-1,3,4-tri-O-acetyl-α-L-fucopyranose (7)*

4.2.7.1. From compound 5. To a suspension of **5** (2 g, 5.77 mmol) in Ac_2O (10 mL, 106 mmol) was added I_2 (0.1 g, 0,4 mmol) and the mixture was stirred for 15 min at room temperature. The obtained solution was diluted with CH_2Cl_2 (50 mL) and washed with an aqueous $Na_2S_2O_3$ solution. The organic layer was separated, the solvent was removed under reduced pressure, the residue was poured into cool water (0–5 °C) and the mixture was stirred for 2 h. After being neutralized to pH 7 with saturated Na_2CO_3 solution, the mixture was extracted with CH_2Cl_2 (3 × 50 mL), the organic extracts were combined, dried over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography (6:1 *n*-hexane/AcOEt), to obtain **7** (Yield: 2.15 g, 98%).

4.2.7.2. From compound 4. To a solution of **4** (2 g, 4.6 mmol) in Ac_2O (4 mL, 42 mmol) was added $HClO_4$–SiO_2 (230 mg) and the reaction mixture was stirred at room temperature for 1 h. After completion, the reaction mixture was diluted with AcOEt (20 mL), filtered through a Celite bed and the filtrate was evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (6:1 *n*-hexane/AcOEt), to obtain **7** (Yield: 1.72 g, 98%).

4.2.7.3. From compound 1. To a solution of 1 (3 g, 7.84 mmol) in MeOH (20 mL), a 0.3 mol/L solution of NaOMe in MeOH (7 mL) was added and the obtained mixture was stirred for 2 h at room temperature. The reaction mixture was neutralized with Amberlite IRA 120 (H^+), the resin was removed by filtration, was washed with MeOH, and the combined filtrates were evaporated to dryness under reduced pressure. The residue was dissolved in DMF (10 mL), benzaldehyde dimethylacetal (1.8 mL, 12 mmol) was added, followed by *p*-toluenesulfonic acid monohydrate (0.15 g, 0.79 mmol) and the obtained mixture was stirred at 50 °C for 1 h and was neutralized with Et_3N. Then the solution was cooled to 0–5 °C, benzyl bromide (1.2 mL, 10.1 mmol) was added followed by a 60% dispersion of NaH in mineral oil (0.4 g, 10.3 mmol) and the mixture was stirred for 1 h at room temperature. After completion of the reaction, MeOH (2 mL) was added, the mixture was diluted with AcOEt (30 mL) and washed with saturated NaCl solution (10 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. Thus, the obtained crude **6** was dissolved in Ac_2O (6.8 mL, 72 mmol), $HClO_4$–SiO_2 (400 mg) was added and the reaction mixture was stirred at room temperature for 1 h. After completion, the reaction mixture was diluted with AcOEt (35 mL), filtered through a Celite bed and the filtrate was evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (6:1 *n*-hexane/AcOEt), to obtain **7** (Yield: 3 g, 80%).

In all the cases **7** was obtained as a syrup: R_f: 0.3 (6:1 *n*-hexane/AcOEt); α **anomer:** ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.40–7.22 (m, 5H, aromatics), 6.38 (d, 1H, $J_{1,2}$ 3.7 Hz, H-1), 5.29 (m, 2H, H-3 and H-4), 4.66 (d, 1H, $J_{H,H'}$ 11.9 Hz, CH_2Ph), 4.56 (d 1H, $J_{H,H'}$ 11.9 Hz, CH_2Ph), 4.23 (dd, 1H, $J_{5,Me}$ 6.4, $J_{5,4}$ 1.2 Hz, H-5), 3.92 (1H, dd, $J_{2,3}$ 10.0, $J_{2,1}$ 3.7 Hz, H-2), 2.14, 2.13, 2.00 [(s, 3H, $COCH_3$) × 3], 1.13 (d, 3H, $J_{Me,5}$ 6.5 Hz; 5-CH_3); ^{13}C NMR ($CDCl_3$, 151 MHz): δ 170.5, 170.2, 169.5, 137.8, 128.5 (2C), 128.1, 127.9 (2C), 90.4, 73.1, 72.4, 71.2, 70.0, 67.2, 21.2, 20.9, 20.7, 16.1.

4.2.8. *2-O-benzyl-3,4-di-O-acetyl-α/β-L-fucopyranose (8)*

4.2.8.1. From compound 6. To a solution of **6** (2.6 g, 6 mmol) in acetone (30 mL) and H_2O (3.4 mL), NBS (3.2 g, 18 mmol) was added and the mixture was stirred for 1 h at room temperature. After completion of the reaction, the obtained solution was diluted with CH_2Cl_2 (130 mL) and successively washed with H_2O (25 mL), aqueous solution of $Na_2S_2O_3$ (15 mL) and H_2O (25 mL). The organic layer was dried over anhydrous Na_2SO_4, the solvents were evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography (2:1 *n*-hexane/AcOEt) to obtain **8** (Yield: 1.87 g, 92%).

4.2.8.2. From compound 7. To a solution of **7** (2 g, 5.26 mmol) in dry DMF (15 mL), hydrazine acetate (0.63 g, 6.84 mmol) was added and the mixture was heated for 30 min at 50 °C (bath temperature). After completion of the reaction, the obtained solution was diluted with AcOEt (30 mL) and was washed with an aqueous saturated solution of NaCl (5 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography (2:1 *n*-hexane/AcOEt) to obtain **8** (Yield: 1.6 g, 90%).

In both cases **8** was obtained as a white solid: mp: 80–82 °C, lit.[6] 80–83 °C; $[\alpha]_D^{25}$ –51.8 (c 1.0, $CHCl_3$), lit.[6] –52.1; Rf: 0.33 (2:1 n-hexane/AcOEt); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.38–7.23 (m, 10H, aromatics), 5.31 (dd, 1H, $J_{3,2}$ 10.3, $J_{3,4}$ 3.4 Hz, H-3α), 5.28 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1α), 5.26 (dd, 1H, $J_{4,3}$ 3.4, $J_{4,5}$ 1.3 Hz, H-4α), 5.19 (dd, 1H $J_{4,3}$ 3.5, $J_{4,5}$ 1.1 Hz, H-4β), 4.97 (dd, 1H, $J_{3,2}$ 10.2, $J_{3,4}$ 3.5 Hz, H-3β), 4.88 (d, 1H, $J_{H,H'}$ 11.6 Hz, CH_2Ph), 4.74 (d, 1H, $J_{1,2}$ 7.6 Hz, H-1β), 4.66 (m, 3H, CH_2Ph), 4.35 (qd, 1H, $J_{5,Me}$ 6.4, $J_{5,4}$ 1.3 Hz, H-5α), 3.82 (dd, 1H, $J_{2,3}$ 10.3, $J_{2,1}$ 3.6 Hz, H-2α), 3.79 (qd, 1H, $J_{5,Me}$ 6.4, $J_{5,4}$ 1.1 Hz, H-5β), 3.57 (dd, 1H, $J_{2,3}$ 10.2, $J_{2,1}$ 7.6 Hz, H-2β), 2.13 (s, 6H, $COCH_3$), 1.99, 1.96 [(s, 3H, $COCH_3$) × 2], 1.18 (d, 3H, $J_{Me,5}$ 6.4 Hz, 5β-CH_3), 1.11 (d, 3H, $J_{Me,5}$ 6.5 Hz, 5α-CH_3); ^{13}C NMR ($CDCl_3$, 151 MHz): δ 170.8, 170.7, 170.3 (2C), 138.4, 137.8, 128.6 (2C), 128.4 (2C), 128.2, 127.8 (5C), 97.5, 91.7, 77.7, 74.8, 74.0, 73.4, 72.9, 71.6, 70.8, 70.1, 69.2, 64.7, 20.9, 20.8, 20.7

(2C), 16.3, 16.1. (NMR data in agreement with reported literature [6]).

4.2.9. *O-(2-O-benzyl-3,4-di-O-acetyl-α/β-L-fucopyranosyl)-trichloroacetimidate (9)*

To a stirred solution of **8** (1.7 g, 5 mmol) and trichloroacetonitrile (2.3 mL, 23 mmol) in dry CH_2Cl_2 (20 mL), DBU (0.15 mL, 1 mmol) was added dropwise. The mixture was stirred for 16 h at room temperature, the solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (6:1 *n*-hexane/AcOEt containing 1% v/v of Et_3N) to obtain **9** (Yield: 2.15 g, 89%) as a mixture of the α and β anomers. Analytical samples of the α and β anomers were obtained by silica gel column chromatography by using the same solvent system.

α anomer: a white solid: mp: 151–153 °C, lit.[6]150–152 °C; $[\alpha]_D^{25}$: 84.6 (c 1.2, $CHCl_3$), lit.[6]–84.9; Rf: 0.55 (4:1 n-hexane/AcOEt); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.34–7.17 (m, 5H, aromatics), 8.55 (s, 1H, NH), 6.47 (d, 1H, $J_{1,2}$ 3.4 Hz, H-1), 5.32 (m, 2H, H-3 and H-4), 4.66 (d, 1H, $J_{H,H'}$ 12.1 Hz, CH_2Ph), 4.59 (d, 1H, $J_{H,H'}$ 12.1 Hz, CH_2Ph), 4.30 (q, 1H, $J_{5,Me}$ 6.5 Hz, H-5), 3.98 (m, 1H, H-2), 2.10, 1.94, [(s, 3H, $COCH_3$) × 2]; 1.10 (d, 3H, $J_{Me,5}$ 6.5 Hz, 5-CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 170.5, 170.1, 161.4, 137.9, 128.5 (2C), 127.9, 127.5 (2C), 94.7, 91.2, 72.9, 72.8, 71.1, 70.0, 67.5, 20.9, 20.7, 16.1. (NMR data in agreement with reported literature [6]).

β anomer: a syrup: Rf: 0.42 (4:1 n-hexane/AcOEt); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 8.69 (s, 1H), 7.34–7.16 (m, 5H, aromatics), 5.77 (d, 1H, $J_{1,2}$ 8.1, H-1), 5.21 (dd, 1H, $J_{4,3}$ 3.5, $J_{4,5}$ 1.2 Hz, H-4), 5.03 (dd, 1H, $J_{3,2}$ 10.1, $J_{3,4}$ 3.5 Hz, H-3), 4.85 (d, 1H, $J_{H,H'}$ 11.4 Hz, CH_2Ph), 4.62 (d, 1H, $J_{H,H'}$ 11.4 Hz, CH_2Ph), 3.88 (m, 2H, H-2 and H-5), 2.12, 1.90 [(s, 3H, $COCH_3$) × 2], 1.18 (d, 3H, $J_{Me,5}$ 6.4, 5-CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 170.6, 169.9, 161.3, 138.0, 128.4 (2C), 127.8 (3C), 98.5, 91.0, 75.6, 75.0, 72.8, 70.6, 70.2, 20.7, 20.6, 16.1. (NMR data in agreement with reported literature [6]).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carres.2020.108221.

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