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Effects of $CoCl_2$ on the regioselective tosylation of oligosaccharides

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ABSTRACT

The tosyl functional group is commonly used in carbohydrate chemistry as a nucleofuge. Tosylation of the primary hydroxyls of carbohydrates are generally performed after orthogonal protection/deprotection reactions. However, it can be done regioselectively from unprotected sugars. Several examples have been described in the literature starting from free monosaccharides. Yields are generally good but may vary according to the nature of the sugar. Starting from free oligosaccharides, the regioselectivity and the yields generally drop significantly. The use of catalysts, such as DMAP or NEt_3, improves the conversion but to the detriment of the regioselectivity. In our current work, we developed a tosylation reaction of the primary positions of several oligosaccharides with improved regioselectivity, using cobalt II chloride in catalytic amounts. Adaptability of this methodology has been tested on cellobiose, maltose, lactose, sucrose and maltotriose.

1. Introduction

In carbohydrate chemistry, tosylation reactions are popular as they are very useful for the preparation of high added value precursors. The introduction of a tosyl functional group is usually achieved by the reaction of a carbohydrate containing a free hydroxyl group with TsCl in pyridine [1]. Depending on the reactivity of the substrate, the reaction conditions can be adapted by selecting the appropriate temperature and stirring time. Catalysts such as DMAP or triethylamine have been used to reduce the reaction times [1,2]. However, when several hydroxyl functions are accessible, this procedure may result in complex mixtures of tosylated products [1,3].

In literature, some examples show the regioselective tosylation of monosaccharides on primary positions starting from unprotected substrates.

In 2017, Chen et al. described the preparation of tosylated monosaccharides (Scheme 1) [4]. After 12 hours of reaction at room temperature, the products were obtained in 62-78 yields. It is important to note that secondary and anomeric positions are not tosylated. On the other hand, similar conditions, applied to free oligosaccharides, are rarely described in literature. In 1982, Gero et al. reported the synthesis of 6,6′-di-*O*-tosyl-D-maltose and 6,6′-di-*O*-tosyl-D-lactose using 3.5 equiv. of TsCl in pyridine at room temperature [5]. After acetylation, the authors obtained the expected products in 40% yield for both maltose and lactose derivatives (purification performed by HPLC). More recently, Oscarson et al. describe the preparation of 1',6,6'-tri-*O*-tosylsucrose and 6,6'-di-*O*-tosyltrehalose in 19% and 16% yields respectively [3]. It appears that the regioselective tosylation of oligosaccharides is more difficult than that of monosaccharides. In order to improve the research currently in progress in our laboratory, we report here a new methodology to obtain better regioselectivity in the tosylation reaction using anhydrous $CoCl_2$ as a catalyst.

2. Results/Discussion

In a first attempt, we reproduced the classical conditions, described by Gero et al., using D-maltose **1** as substrate [5]. Several experimental conditions were evaluated, including TsCl equivalents, temperature and stirring time. All these results are summarized in Table 1.

The first attempts (Entry 1) were carried out by slowly adding 4 equiv. of TsCl in a solution of maltose in dry pyridine at 0°C. The mixture was then gradually warmed up to room temperature. The reactions were monitored by TLC, mass spectrometry and 1D NMR, between 2 and 24 hours of stirring. It is evident that, despite the use of an excess of TsCl (Entry 1), the conversion remains

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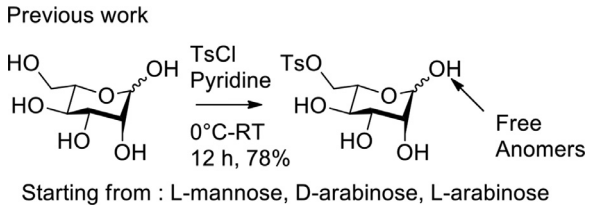


Scheme 1. Some examples of monotosylation on monosaccharide from Chen et al. [4]

limited and unreacted maltose was still present in a significant amount.

In addition to an incomplete conversion, the reaction mixture contains monotosylated maltose and polytosylated derivatives. The desired compound **2**, was obtained as a minor product in a mixture of several polytosylated derivatives, making its purification ineffective on silica gel, even after *per*acetylation. Therefore, under these classical conditions, the yields previously reported could not be achieved. To improve the conversions of our next trials, we drew inspiration from the literature. Recently, Krause et al. observed a significant improvement of the ditosylation reaction on β-azido-D-maltoside using $ZnBr_2$ [6]. However, using free maltose **1** as substrate, no difference was noted in comparison with entry 1. Only the addition of triethylamine to the medium (Entry 2) increased our conversions. Using 4 equiv. of anhydrous NEt_3, no traces of free maltose were detected after 2 hours of reaction. Thereafter, the 24-hour reaction monitoring showed no significant changes. Despite the complexity of the mixture, we were able to perform a purification of the ditosylated derivative **2** on silica gel, bringing the yield to 23%. It is interesting to note that reducing the temperature to 8°C did not sufficiently reduce the presence of polytosylated compounds [2,7].

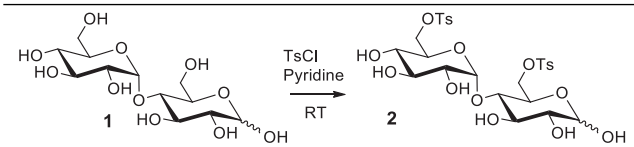
In view of the difficulties of purification, and the low yields of product **2**, we decided to carry out a final optimization by adapting the conditions described by Tatsuta et al. in 1967 [8]. The authors obtained 45% of *per*acetyl-6,6′-di-*O*-tosyl-D-maltose using Drierite®. After adding Drierite® in our conditions, we noticed a drastic decrease in the formation of polytosylated products by mass spectrometry. Using triethylamine, in the presence of blue Drierite® (Entry 3), we obtained 53% of compound **2** (major product) after purification on silica gel. Surprisingly, using white Drierite® without color indicator (Entry 4), the reaction led to a complex mixture.

These results suggested that the color indicator, i.e. $CoCl_2$, was at the origin of the higher regioselectivity of the tosylation. Knowing that cobalt (II) chloride has been described in previous works for the catalysis of regioselective acetylations and also in tosylation reactions of some aliphatic and aromatic alcohols with TsOH, further reactions were carried out using anhydrous $CoCl_2$ [9–11]. After optimization of the conditions, 4 equiv. of NEt_3 and 0.6 equiv. of $CoCl_2$, in anhydrous pyridine, led to the total conversion and we obtained 75% of compound **2** after only 2 hours at room temperature (Entry 5). Monotosylated and polytosylated derivatives were only observed in trace amounts by NMR. Encouraged by these results, we extended this methodology to other disaccharides as well as to maltotriose (Table 2).

All the products described in the table above were obtained after purification on silica gel chromatography without prior *per*acetylation. In all cases, mass spectrometry analyses of the reaction mixture clearly indicate a significant decrease in the amount of polytosylation products when using $CoCl_2$. The tosylation reaction appears to be more selective for primary positions. Starting from lactose **3**, the reaction has to be stirred only 15 min. to avoid further tosylations. Sucrose **5** has also been tested, which led to the formation of 1',6,6'-tri-*O*-tosylsucrose **6** and 1',2,6,6'-tetra-*O*-tosylsucrose **7** in 41 % and 34 % yields respectively. The position of the fourth tosyl functional group has been identified using 13C NMR spectroscopy which indicates a deshielding effect on carbon C2 from compound **6** to compound **7** (72.2 to 79.2 ppm). This observation has been confirmed by 1H NMR analyses. In the case of cellobiose, our experimental conditions did not lead to the formation of the expected product, but to a complex mixture that we failed to analyze the nature. In contrast, the reaction of methyl-cellobioside **8** was more efficient. We thus obtained the product **9** in 66% yield after 30 min of stirring. In some cases, the anomeric position may be involved in the formation of side products that have not been identified. Finally, we decided to try the tosylation of maltotriose **10**, a trisaccharide. Using 1.75 equiv. *per* OH of both TsCl and Et_3N in the presence of $CoCl_2$, we observed the formation of the desired compound **11** in 50% yield after purification. This compound has never been described in the literature and may be of importance for the preparation of molecules of higher added value, such as those described in our previous work [12].

Based on all the tests performed, we hypothesize that Co II chelates the secondary hydroxyl groups, limiting their substitution. Further researches are currently being carried out in our laboratory to establish the precise role of cobalt salts in these reactions.

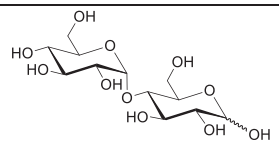
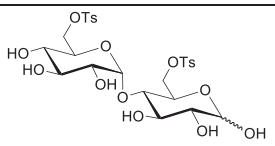
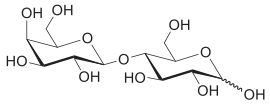
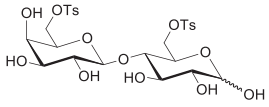
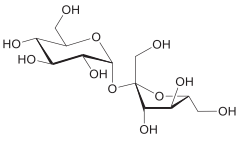
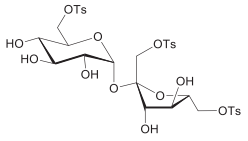
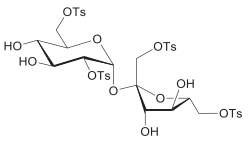
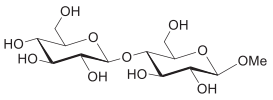
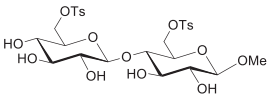
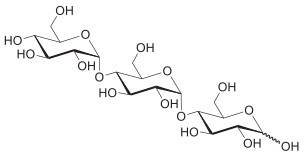
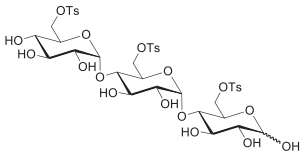
Table 1
Regioselective tosylation of D-maltose **1**.



Entry	Time	Additive	Compound **2**
1	2->24 h	-	Complex mixture
2	2->24 h	NEt_3	23%
3	2->24 h	NEt_3 + blue Drierite®[a]	53%
4	2->24 h	NEt_3 + white Drierite®[d]	Complex mixture
5	2 h	NEt_3 + $CoCl_2$[c]	75%

Reaction conditions: Using D-maltose, 4 equiv. of TsCl were used in dry pyridine at room temperature. 4 equiv. of NEt_3 were used for entries 2, 3, 4, and 5.
[a] Drierite® (anhydrous calcium sulfate containing 97% $CaSO_4$ and 3% $CoCl_2$ as color indicator)
[d] Drierite® without color indicator
[f] 0.6 equiv. of $CoCl_2$ (0.3 equiv. *per* OH)

Table 2
Regioselective tosylation on oligosaccharides.

Substrat	Product	Time	Yield
 **1**	 **2**	120 min.	75%
 **3**	 **4**	15 min.	54%
 **5**	 **6**	30 min.	41% (litt. 19%)[a] [3]
	 **7**		34% (litt. 13%)[a] [3]
 **8**	 **9**	30 min	66 % (litt. 11%)[a] [3]
 **10**	 **11**	1 h	50 %

Reaction conditions: Oligosaccharides were diluted in dry pyridine and anhydrous $CoCl_2$ (0.3 equiv. *per* primary OH) was added. The reaction mixture was cooled to 0°C before the addition of TsCl (2 equiv. *per* OH for maltose and 1.75 equiv. *per* OH for the others) and Et_3N (same quantity as for TsCl). Then temperature was gradually increased to RT and the reaction stirred for the time indicated in the table above. [a] Preparation of compounds **6, 7** and **9** has been described in literature but not fully characterized.

3. Conclusion

We developed a regioselective tosylation of primary positions of di-and trisaccharides by using $CoCl_2$ in catalytic amounts with triethylamine, and pyridine as solvent. This addition minimizes the formation of polytosylated products and improves the yields of selective tosylated compounds.

4. Financial support

We thank the Ministère français de l'Enseignement supérieur, de la Recherche et de l'Innovation for the financial support.

5. Experimental Section

All reagent-grade chemicals were obtained from commercial suppliers and were used as received. Cobalt (II) chloride purum p.a., anhydrous (98.0%) was purchased from Sigma-Aldrich (CAS # 7646-79-9), and was used as received without further purification process. Characterizations of known compounds were in accordance with literature. Optical rotations were recorded in MeOH solution. FTIR spectra were obtained using ATR and are reported in cm^{-1}. ^1H NMR (400 and 600 MHz) and ^{13}C NMR (101 and 151 MHz) spectra were recorded in MeOD . The proton and carbon signal assignments were determined from decoupling experiments, COSY, HSQC, HMBC spectra. TLC were performed on Silica F254 and detection by UV light at 254 nm or by charring with cerium molybdate reagent. Column chromatography was performed on Silica Gel 60 (230 mesh). High-resolution electrospray mass spectra in the positive ion mode were obtained on a Q-TOF Ultima Global hybrid quadrupole/time-of-flight instrument, equipped with a pneumatically assisted electrospray (Z-spray) ion source and an additional sprayer (Lock Spray) for the reference compound. The source and desolvation temperatures were kept at 80 and 150°C, respectively. Nitrogen was used as the drying and nebulizing gas at flow rates of 350 and 50 L/h, respectively. The capillary voltage was 3.5 kV, the cone voltage 100 V and the RF lens1 energy was optimized for each sample (40 V). For collision-induced dissociation (CID) experiments, argon was used as collision gas at an indicated analyser pressure of 5.10^{-5} Torr and the collision energy was optimized for each parent ion (50-110 V). Lock mass correction, using appropriate cluster ions of sodium iodide $(NaI)_nNa^+$, was applied for accurate mass measurements. The mass range was typically 50-2050 Da and spectra were recorded at 2 s/scan in the profile mode at a resolution of 10000 (FWMH).

*5.1. Synthesis of 6,6'-di-O-tosyl-D-maltose (**2**)*

To a solution of D-maltose monohydrate **1** (3.15 g, 8.75 mmol) in dry pyridine (50 mL), anhydrous cobalt (II) chloride (0.6 equiv.,

0.68 g, 5.25 mmol) was added and the reaction mixture was cooled to 0°C. Then *p*-toluenesulfonyl chloride (4 equiv., 6.66 g, 35.07 mmol) and anhydrous triethylamine (4 equiv., 4.88 mL, 35.07 mmol) were slowly added and the reaction mixture stirred at room temperature for 120 min. The reaction was then quenched using methanol (150 mL). After stirring for 5 min., the mixture was concentrated to dryness in vacuo and purified over silica gel column chromatography (gradient from cyclohexane/EtOAc (2/3; v/v) to EtOAc/Methanol (8/2; v/v). The desired product **2** was isolated as a white solid containing the two anomers (4.25 g, 75%, α/β: 65/35). R_f (EtOAc/Methanol, 7/3, v/v) 0.5; ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.81 – 7.76 (m, CH-Ar, 6.9H), 7.41-7.44 (m, CH-Ar, 7.8H), 4.98 (d, J = 3.7 Hz, H1α, 1H), 4.94 (d, J = 3.8 Hz, H1'β, 0.6H), 4.91 (d, J = 3.8 Hz, H1'α, 1.1H), 4.43 (d, J = 7.8 Hz, H1β, 0.6H), 4.35 – 4.08 (m, H6α, H6β, H6'α, H6'β, 7.1H), 3.93-3.96 (m, H5α, 1H), 3.82 (t, J = 9.3 Hz, H3α, 1.1H), 3.81-3.64 (m, 1.78H, H5'α, H5'β, 1.8H), 3.56-3.51(m, H5β, H3β, H3'α, H3'β, 3.2H), 3.34 – 3.24 (m, H2α, H4'α, H4β, H4'β, H4α, H2'α, H2'β, 7.8H), 3.12 (dd, J = 9.5, 7.7 Hz, H2β, 0.6H), 2.46 (s, CH_3, 7.34H), 2.45 (s, CH_3, 2.7H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 146.5 (C-Ar), 146.4 (C-Ar), 134.3 (C-Ar), 134.3 (C-Ar), 134.1 (C-Ar), 131.1 (CH-Ar), 131.0 (CH-Ar), 131.0 (CH-Ar), 130.9 (CH-Ar), 129.1 (CH-Ar), 129.1 (CH-Ar), 129.0 (CH-Ar), 129.0 (CH-Ar), 102.8 (C1'β; C1'α), 98.0(C1β), 93.6 (C1α), 81.9, 81.5, 77.5, 75.4, 74.8, 74.7, 74.3, 73.8, 73.6, 73.0, 72.2, 72.2, 70.5, 70.2 (C2, C3, C5, C2', C4'), 70.8, 70.4, 70.3 (C6α, C6β, C6'α, C6'β), 69.1 (C5α), 21.6 (CH_3). IR (ATR) ν = 3437, 2937, 1598, 1450, 1354, 1174, 1055, 1018, 931, 813 cm^{-1}; HRMS (CI, NH_3): MNa^+, found 673.1251. $C_{26}H_{34}O_{15}NaS_2$ requires 673.1237.

5.2. Synthesis of 6,6'-di-O-tosyl-D-lactose (**4**)

Compound **4** was prepared as described for compound **2** starting from D-lactose monohydrate **3** (0.52 g, 1.46 mmol) in dry pyridine (15 ml), 0.6 equiv. of anhydrous cobalt chloride (0.11 g, 0.87 mmol), 3.5 equiv. of both tosylchloride (0.97 g, 5.13 mmol) and anhydrous triethylamine (0.71 ml, 5.13 mmol). After 15 min. of stirring, the reaction mixture was treated as described previously. The mixture was purified over silica gel column chromatography (gradient from cyclohexane/EtOAc (1/1, v/v) to EtOAc/Methanol (8/2: v/v). The desired product **4** was isolated as a white solid containing the two anomers (0.51 g, 54 %, α/β: 60/40). R_f (EtOAc/Methanol, 7/3, v/v) 0.6; ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.92 – 7.76 (m, CH-Ar, 9.6H), 7.51 – 7.39 (m, CH-Ar, 9.9H), 5.01 (d, J = 3.8 Hz, H1α, 1H), 4.50 – 4.43 (m, H1β, 1.5H), 4.42 – 4.00 (m, H6α, H6β, H6'α, H6'β, H1'α, H1'β, H5α, 10.8H), 3.82 – 3.71 (m, H5'α, H5'β, H3'α, H3'β, 5.1H), 3.68 – 3.58 (m, H5β, 0.8H), 3.52 – 3.44 (m, H3α, H3β, H2'α, H2'β, 3.1H), 3.43 – 3.31 (m, H4α, H4β, H2α, H4'α, H4'β, 11.9H), 3.18 (t, J = 8.4 Hz, H2β, 0.7H), 2.46 (s, CH_3, 8.3H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 146.7 (C-Ar), 146.4 (C-Ar), 146.3 (C-Ar), 134.5 (C-Ar), 134.3 (C-Ar), 133.9 (C-Ar), 133.9 (C-Ar), 131.2 (CH-Ar), 131.0 (CH-Ar), 131.0 (CH-Ar), 130.9 (CH-Ar), 129.2 (CH-Ar), 129.2 (CH-Ar), 129.1 (CH-Ar), 104.4, 104.3 (C1'), 97.9, 93.5 (C1), 80.3, 79.8 (C4), 75.8, 75.6, 74.1, 73.9, 73.9, 73.5, 73.1, 72.6, 71.8, 71.7, 69.6, 68.8 (C2, C3, C5, C2', C3', C4', C5'), 70.5, 70.1, 70.1 (C6, C6'), 21.6 (CH_3); IR (ATR) ν = 3437, 2924, 1612, 1355, 1174, 1070, 1022, 825 cm^{-1}; HRMS (CI, NH_3) MNH_4^+, found 668.1683. $C_{26}H_{34}NO_{15}S_2$ requires 668.1686.

5.3. Synthesis of 1',6,6'-tri-O-tosylsucrose (**6**)

Compound **6** was prepared as described previously, starting from powdered sucrose **5** (0.5 g, 1.46 mmol) in dry pyridine (15 ml). If needed, this solution can be heated for 15 min. at 60°C until complete dissolution. Then 0.9 equiv. of anhydrous cobalt II chloride (0.17 g, 1.31 mmol) and 5.25 equiv. of both tosylchloride(1,5 g, 7,66 mmol) and anhydrous triethylamine(0,98 ml, 7.66 mmol) were added. After stirring for 30 min., the reaction mixture was quenched using methanol, concentrated to dryness in vacuo and dissolved in DCM. The solution was washed three times with water, dried over sodium sulfate, filtered and concentrated. A purification over silica gel column chromatography (gradient from cyclohexane/EtOAc (1/1, v/v) to EtOAc/Methanol (9/1, v/v) led to the desired product **6**, isolated as a white solid (0.48 g, 41 %). *Compound **6**:* R_f (EtOAc/Methanol, 9/1, v/v) 0.63; ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.86 – 7.73 (m, CH-Ar, 6H), 7.52 – 7.38 (m, CH-Ar, 6H), 4.65 (d, J = 3.9 Hz, H1, 1H), 4.32 – 4.28 (m, H6, 2H), 4.17 – 4.12 (m, H6', 1H), 4.05 (d, J = 11.4 Hz, H3', 1H), 3.99 (dd, J = 9.5, 6.7 Hz, H1', 1H), 3.88 (d, J = 8.9 Hz, H5, 1H), 3.81 (t, J = 8.7 Hz, H4', 1H), 3.69 (td, J = 8.8, 1.9 Hz, H5', 1H), 3.51 (dd, J = 9.8, 8.9 Hz, H3, 1H), 3.13 (dd, J = 9.8, 3.9 Hz, H2, 1H), 3.02 (dd, J = 9.8, 8.8 Hz, H4, 1H), 2.53 – 2.46 (m, CH_3, 9H); ^{13}C NMR (151 MHz, Methanol-d_4) δ 146.6 - 134.0 (C-Ar), 131.1 - 129.0 (CH-Ar), 103.0 (C2'), 92.7 (C1), 80.80 (C5'), 77.1 (C3'), 74.8 (C4'), 74.3 (C3), 72.8 (C6), 72.2 (C2), 71.8 (C5), 71.52 (C4), 71.1 (C6'), 68.3 (C1'), 21.6, 21.6, 21.6 (CH_3); IR (ATR) ν = 2532, 1598, 1450, 1355, 1174, 974, 813 cm^{-1}; $[\alpha]_D^{20}$ +56.2 (c 0.5, MeOH); HRMS (CI, NH_3) MNa^+: found 827.1334. $C_{33}H_{40}O_{17}NaS_3$ requires 827.1325; *1',2,6,6'-tetra-O-tosylsucrose* **7** were also isolated during this process as a white solid (0.48 g, 34 %). R_f (EtOAc/Methanol, 9/1, v/v) 0.77; ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.93 – 7.86 (m, CH-Ar, 6H), 7.70 (d, J = 8.4 Hz, CH-Ar, 2H), 7.56 – 7.39 (m, CH-Ar, 8H), 4.91 (d, J = 3.7 Hz, H1, 1H), 4.32 (dd, J = 10.4, 1.7 Hz, H6, 1H), 4.28 – 4.18 (m, H6, H6', 2H), 4.14 – 4.07 (m, H1', H6', 2H), 4.00 – 3.76 (m, H2, H5, H1', H5', H4', H3', 6H), 3.66 (dd, J = 9.8, 8.8 Hz, H3, 1H), 3.01 (dd, J = 10.0, 8.8 Hz, H4, 1H), 2.55 – 2.47 (m, CH_3, 12H); ^{13}C NMR (151 MHz, Methanol-d_4) δ 146.8 - 133.7 (C-Ar), 131.2 - 129.0 (CH-Ar), 103.2 (C2'), 90.5 (C1'), 80.8 (C5'), 79.2 (C2), 76.7 (C3'), 74.5(C4'), 72.6 (C6'), 71.6 (C5), 71.4 (C4), 71.2 (C3), 70.8 (C6), 68.0 (C1'), 21.8, 21.7, 21.7 (CH_3); IR (ATR) ν = 3522, 1597, 1357, 1174, 1097, 975, 813 cm^{-1}; $[\alpha]_D^{20}$ +48.6 (c 0.5, MeOH); HRMS (CI, NH_3) MNH_4^+: found 976.1860. $C_{40}H_{50}NO_{19}S_4$ requires 976.1860.

5.4. Synthesis of Methyl-6,6'-di-O-tosyl-β-cellobioside (**9**)

Compound **9** was prepared as described previously, starting from compound **8** (2 g, 5.61 mmol) in dry pyridine (60ml), 0.6 equiv. of anhydrous cobalt II chloride (0.43 g, 3.36 mmol), 3.5 equiv. of both tosylchloride (3.73 g, 19 mmol) and anhydrous triethylamine (2.73 ml, 19 mmol). After stirring for 30 min, the reaction mixture was treated as described previously. The mixture was purified over silica gel column chromatography (gradient from pure EtOAc to EtOAc/Methanol (9/1, v/v). The desired product **9** was isolated as a white solid (2.44 g, 66%). R_f (EtOAc/Methanol, 7/3, v/v) 0.65; ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.97 – 7.81 (m, CH-Ar, 4H), 7.56 – 7.41 (m, CH-Ar, 4H), 4.54 – 4.34 (m, H6, H6', 3H), 4.31 (d, J = 7.9 Hz, H1', 1H), 4.23 – 4.14 (m, H1, H6, H6', 2H), 3.71 – 3.14 (m, H2, H3, H4, H5, H2', H3', H4', H5', OCH_3, 11H), 2.51 (s, Ar-CH_3, 6H); ^{13}C NMR (101 MHz, Methanol-d_4) δ 146.6 (C-Ar), 146.4 (C-Ar), 134.2 (C-Ar), 134.0 (C-Ar), 131.15 (CH-Ar), 131.04 (CH-Ar), 129.12 (CH-Ar), 129.09 (CH-Ar), 129.05 (CH-Ar), 104.8 (C1'), 103.7 (C1), 79.8, 77.3, 75.4, 75.1, 74.4, 74.2, 73.3, 70.8 (C2, C3, C4, C5, C2', C3', C4', C5'), 70.3 (C6, C6'), 70.0 (C6, C6'), 57.2 (OCH_3), 21.6 (CH_3); $[\alpha]_D^{20}$ = -4.00 (c 0.5, MeOH); IR (ATR) ν = 2989, 2519, 1355, 1174, 1053, 975, 929, 815, 790 cm^{-1}. HRMS (CI, NH_3): MNH_4^+ found, 682.1839. $C_{27}H_{40}NO_{15}S_2$ requires 682.1842.

5.5. Synthesis of 6,6',6''-tri-O-tosyl-D-maltotriose (**11**)

The trisaccharide **11** was prepared as described before, starting from maltotriose **10** (0.5 g, 0.99 mmol) in dry pyridine (10ml), 0.9

equiv. of anhydrous cobalt II chloride (0.115 g, 0.89 mmol), 5.25 equiv. of both tosylchloride (1.88 g, 5.20 mmol) and anhydrous triethylamine (0.83 ml, 5.20 mmol). After stirring for 60 min., the reaction mixture was quenched with methanol, concentrated to dryness in vacuo and dissolved into DCM. The solution was washed three times with water, dried over sodium sulfate, filtered and concentrated. A purification over silica gel column chromatography (gradient from cyclohexane/EtOAc (1/1, v/v) to EtOAc/Methanol (9/1, v/v) led to the desired product **11** as a white solid (0.48 g, 50 %, α/β: 70/30). Rf: 0.6 (EtOAc:Methanol; 9:1; v:v). ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.88 – 7.79 (m, CH-Ar, 10H), 7.49 – 7.42 (m, CH-Ar, 10.3H), 5.03 (d, J = 3.7 Hz, H1α, 1H), 4.98 (dd, J = 23.2, 3.7 Hz, H1'α, H1'β, H1''α, H1''β, 3.1H), 4.51 – 4.16 (m, H1β, H6α, H6β, H6'α, H6'β, H6''α, H6''β, 9.4H), 4.03 – 3.96 (m, H5α, 1H), 3.92 – 3.54 (m, H5β, H5'α, H5'β, H5''α, H5''β, H3'α, H3'β, H3''α, H3''β, 8.2H), 3.47 – 3.28 (m, H4'α, H4'β, H4''α, H4''β, H4α, H4β, H2α, H2β, H2'α, H2'β, H2''α, H2''β, 10.7H), 3.17 (dd, J = 9.5, 7.8 Hz, H2β, 0.53H), 2.50 (s, CH_3, 5.3H), 2.48 (d, J = 2.6 Hz, CH_3, 9H); ^{13}C NMR (151 MHz, Methanol-d_4) δ 146.5 (C-Ar), 146.4 (C-Ar), 146.4 (C-Ar), 146.3 (C-Ar), 134.4 (C-Ar), 134.3 (C-Ar), 134.2 (C-Ar), 134.2 (C-Ar), 134.1 (C-Ar), 131.1 (CH-Ar), 131.0 (CH-Ar), 131.0 (CH-Ar), 131.0 (CH-Ar), 131.0 (CH-Ar), 129.1 (CH-Ar), 129.1 (CH-Ar), 129.0 (CH-Ar), 129.0 (CH-Ar), 102.7-102.3 (C1', C1''), 97.9, 93.6 (C1), 81.7, 81.1, 80.1 (C4, C4'), 77.4, 75.4, 74.7, 74.4, 74.4, 74.2, 73.7, 73.6, 73.3, 73.1, 73.0, 72.2, 72.1, 70.8, 70.5 (C2, C3, C5, C2', C3', C5', C2'', C3'', C4'', C5''), 70.75, 70.47, 70.41, 70.31 (C6, C6', C6''), 69.0 (C5), 21.6 (CH_3); IR (ATR) ν = 3369, 2935, 1577, 1354, 1174, 1018, 1001, 931, 815 cm^{-1}; HRMS (CI, NH_3) MNa^+: found 989.1871. $C_{39}H_{50}O_{22}NaS_3$ requires 989.1854.

CRediT authorship contribution statement

Jamal El-Abid: Investigation, Experimental work, Characterization of compounds, Writing - review & editing.

Vincent Chagnault: Conceptualization, Methodology, Writing - review & editing, Writing - original draft, Formulation of hypothesis, Design of analytical experiments, Supervised this work.

José Kovensky: Conceptualization, Methodology, Writing - review & editing, Project administration.

Vincent Moreau: Writing - review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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