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Synthesis of 4-thiol-furanosidic uronate *via* hydrothiolation reaction†

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Uronic acids are not only important building blocks of polysaccharides and oligosaccharides but also are widely used in the food and pharmaceutical industries. Inspired by the structure of natural products, here, we disclosed base-mediated and radical-mediated hydrothiolation reactions for the preparation of thiol-contained uronates. In comparison with base-mediated reaction, radical-mediated hydrothiolation is inefficient due to the electron-withdrawing group on the ethylene group; nevertheless, the adduct had excellent stereoselectivity at both C-4 and C-5 positions. For the alkaline approach, thiols as nucleophiles can regioselectively and stereoselectively attach to the C-4 position of $\Delta^{-4,5}$-unsaturated uronate with moderate to good yields. However, poor stereoselectivity at the C-5 position was observed due to retro thiol-Michael addition. After removing the protecting group of the thiol, the thiol adduct was isomerized to the furanosidic form and the 4-thiol-furanosidic uronate derivative was synthesized for the first time.

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1. Introduction

Uronic acids are a group of monosaccharides including L-arabinuronic acid, D-xyluronic acid, D-galacturonic acid, D-glucuronic acid and D-mannuronic acid, and are important building blocks for polysaccharides and oligosaccharides, such as glycosaminoglycans, pectic acid, and alginate *etc.*, which represent an important class of biologically relevant molecules (Fig. 1A).[1] For example, these polysaccharides participate in the immune response,[2] bacterial pathogenesis,[3] and cancer progression and metastasis[4] and can be found on cell surfaces as well as in the extracellular matrix of eukaryotes. Among the uronic acids, D-galacturonic acid and D-glucuronic acid, in particular, are widely used in the food and detergent industries as well in medicine.[5,6] For instance, D-glucuronic acid can be used as a detergent for removing calcareous and rust deposits from metals or other surfaces owing to its ability for chelating metals. D-Galacturonic-metal complexes can also be used as potential anti-cancer drugs and as cosmetics for protecting skin from the damage of UV radiation.[7,8]

Enzymatic digestion and acid hydrolysis were applied for the preparation of valuable uronic acids.[9] For the enzymatic approach, two enzymatic reactions, namely hydrolysis, and lytic β-elimination, are involved in the depolymerization of polysaccharides.[10] The hydrolytic pathway is utilized by eukaryotic enzymes and lytic β-elimination is employed by the enzymes of bacterial or fungal. The lyase breaks the glycosidic backbone through a β-eliminative cleavage generating an $\Delta^{4,5}$-unsaturated uronic acid (ΔUA) at the non-reducing terminus of digested polysaccharides (Fig. 1B).

This unique feature of ΔUA provides an opportunity for the functionalization of uronic acid *via* base- or radical-mediated hydrotholation reaction, which are highly efficient click reactions and have been widely used in applied sciences.[11] In this way, we can prepare diverse uronic acid analogs, *S*-linked glycosides in particular, for exploring the application and for understanding the mechanism of enzymatic reaction.[12]

Generally, *S*-, *N*- or *C*-linked glycosides as carbohydrate mimics are focused synthetic targets in biological studies and leads to drug discovery because that they display lower susceptibility to enzymatic and acid hydrolysis.[13,14] However, *S*-linked glycosides compared with *N*- and *C*-linked glycosides are more attractive due to ease preparation.[15] Although the bond length of the C–S single bond is longer than the C–O single bond, the C–S–C bond angle is significantly smaller than the C–O–C angle, which often results in relatively small differences between the position of the carbon atoms of the glycosidic linkage.[16] Besides, *S*-linked glycosides represent a similar conformational preference to natural glycosides when in solution and when complexed with a protein.[17–20] As a result, we aimed to reveal the reactivity of ΔUA as a starting compound towards the synthesis of complex *S*-linked glycosyl products.

Herein, both alkaline and radical conditions were applied for the construction of *S*-linked uronate derivatives. The utility of basic condition with thiophenol (PhSH) or mercaptobenzyl (BnSH) as nucleophiles resulted in moderate to high yields with C-4 stereoselectivity. The poor stereoselectivity of adducts at the C-5 position

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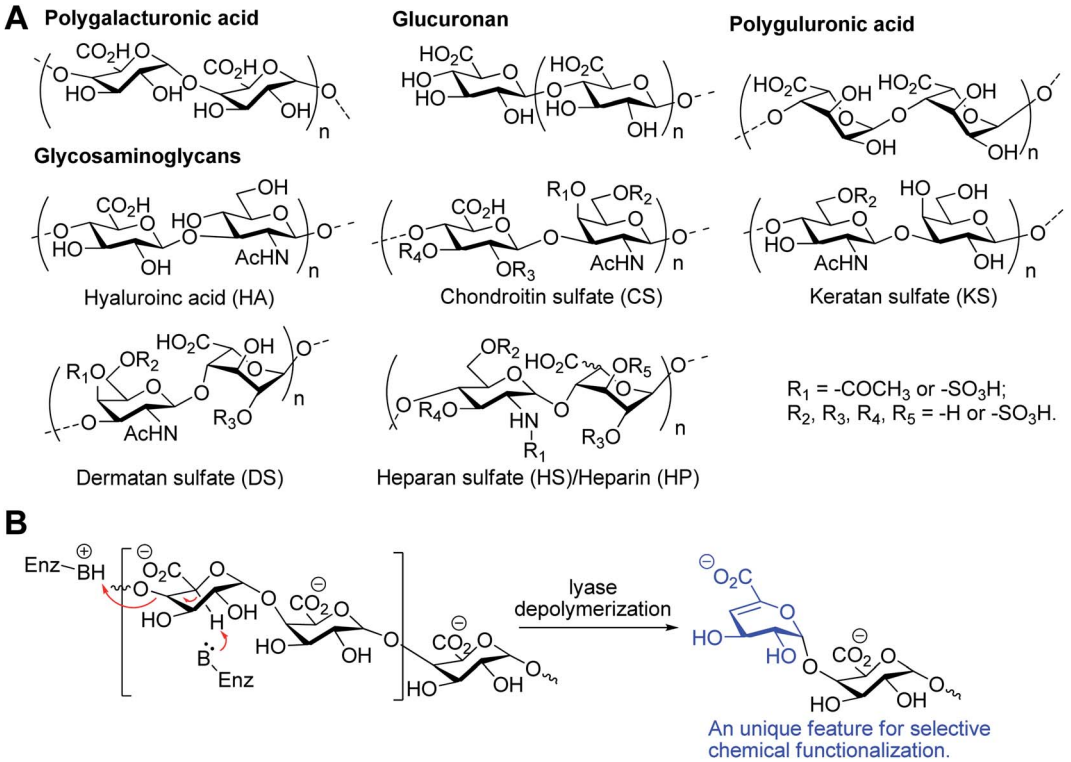


Fig. 1 The structure of uronic acid contained biologically relevant molecules (A) and the general mechanism of the enzymatic β-elimination reaction (B).

is due to the retro thiol-Michael addition. In a comparison with the alkaline condition, radical-mediated hydrothiolation reaction gave a product with specific stereoselectivity at both C-4 and C-5 position, however, the overall yield was low. After deprotection of the benzyl group, a 4-thiol-furanosidic uronate derivative was obtained and the preparation of 4-thiol-furanosidic uronate derivative was firstly reported here.

2. Materials and methods

2.1 General experimental procedures

Solvents and chemicals were purchased from commercial suppliers and used as received. Compounds **1β** were prepared according to literature procedures and the detailed information was shown in the ESI.†[21] ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance III 300 MHz and a Bruker Avance III HD-600 MHz instrument. NMR spectra were recorded in $CDCl_3$, and chloroform signals ($\delta = 7.26$ ppm in ^{1}H NMR; $\delta = 77.16$ ppm in ^{13}C NMR) were used as an internal standard. Splitting patterns are reported as following: s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet. Coupling constants (J) are reported in Hz. IR spectra were recorded with a PerkinElmer Spectrum 100 FTIR spectrometer and data are reported in cm^{-1}. High-resolution mass spectrometry (HRMS) was carried out with an AB SCIE X QSTAR® XL spectrometer (ESI-MS). Liquid chromatography-mass spectrometry (LC-Mass) was measured on a Thermo TSQ-20002 Triple-Q spectrometer. Optical rotations were measured with a Horiba SEPA-300 digital polarimeter. TLC was carried out on pre-coated sheets (Merck Art. 60 F_{254}, 0.25 mm). Reaction products were isolated by flash chromatography on FUJI silysia chemistry MB-70-40/75 silica gel. Reverse-phase high-performance liquid chromatography (Shimadzu LC-20AD) was employed to determine the ratio of products by using Platisil 5 μm PH column (150 mm × 4.6 mm). Yields of products refer to chromatographically purified products unless otherwise stated. Dichloromethane was dried with CaH_2 (5% wt.) then distilled under N_2. *N*,*N*-Dimethylformamide, acetone, toluene, and methanol were dried with 4 Å or 3 Å molecular sieves. All reactions were carried out under N_2 or Ar.

2.2 General protocol for base-mediated thiol-Michael addition

To a solution of $\Delta^{4,5}$-unsaturated uronate derivative, **1β** (1 equiv.) in CH_3CN at a final concentration of 0.2 M was added bases (1 equiv.) and thiols (10 equiv.). The reaction was stirred at 60 or 80 °C for 18 h. Then, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography giving desired products.

It is worth notice that the starting material **1β** was not fully consumed during the reaction. The reaction condition leading to the best conversion yield of **1β** was around 80% and that could be recovered after flash column chromatography. The ratio of desired products was determined by high-performance liquid chromatography (HPLC) analysis (0.1% formic acid and a 50 to 100% acetonitrile gradient on Platisil 5 μm PH column).

2.2.1 Methyl (methyl-2,3-di-*O*-acetyl-4-mercaptophenyl-β-D-galactopyranosid) uronate (I). $R_f = 0.35$ (EtOAc : *n*-Hex = 1 : 2 v/v).; $[\alpha]_{589}^{25} = +17.0°$ ($c = 0.5$, $CHCl_3$).; ^1H NMR (300 MHz, $CDCl_3$, 297 K): $\delta = 7.47–7.44$ (m, 2H, Ar), 7.31–7.23 (m, 3H, Ar), 5.43 (dd, $J_1 = 10.1$ Hz, $J_2 = 7.9$ Hz, 1H, H_2), 5.10 (dd, $J_1 = 10.1$ Hz, $J_2 = 4.4$ Hz, 1H, H_3), 4.50 (d, $J = 2.1$ Hz, 1H, H_5), 4.40 (d, $J = 7.9$ Hz, 1H, H_1), 4.23 (dd, $J_1 = 4.3$ Hz, $J_2 = 2.1$ Hz, 1H, H_4), 3.79 (s, 3H, OMe), 3.58 (s, 3H, OMe), 2.08 (s, 3H, OAc), 1.62 (s, 3H, OAc) ppm.; ^{13}C NMR (75 MHz, $CDCl_3$, 295 K): δ = 170.60, 169.46, 167.60, 134.80, 132.44, 129.15, 127.67, 102.51, 73.88, 73.24, 69.15, 57.12, 52.74, 52.51, 20.94, 20.24 ppm.; IR (KBr): 3003, 2853, 1759, 1744, 1481, 1377, 1234, 1111 743 cm^{-1}.; HRMS (ESI) *m*/*z*: calcd for $C_{18}H_{22}O_8SNa^+$ $[M + Na]^+$: 421.0933, found: 421.0936.

2.2.2 Methyl (methyl-2,3-di-*O*-acetyl-4-mercaptophenyl-β-l-altropyranosid) uronate (II). $R_f = 0.63$ (EtOAc : *n*-Hex = 1 : 2 v/v).; $[\alpha]_{589}^{25} = -103.5°$ (c = 0.5, $CHCl_3$).; ^1H NMR (300 MHz, $CDCl_3$, 294 K): $\delta = 7.44–7.40$ (m, 2H, Ar), 7.34–7.27 (m, 3H, Ar), 5.17 (dd, $J_1 = J_2 = 3.5$ Hz, 1H, H_3), 4.92 (dd, $J_1 = 3.7$ Hz, $J_2 = 1.7$ Hz, 1H, H_2), 4.70 (d, d, $J = 1.7$ Hz, 1H, H_1), 4.65 (d, $J = 10.1$ Hz, 1H, H_5), 3.76 (dd, $J_1 = 10.1$ Hz, $J_2 = 3.3$ Hz, 1H, H_4), 3.61 (s, 3H, OMe), 3.41 (s, 3H, OMe), 2.11 (s, 3H, OAc), 2.08 (s, 3H, OAc) ppm.; ^{13}C NMR (75 MHz, $CDCl_3$, 296 K): $\delta = 170.00$, 169.52, 169.38, 133.27, 132.61, 129.29, 128.10, 98.59, 69.46, 69.37, 67.78, 56.26, 52.54, 46.96, 21.10, 20.81 ppm.; IR (ATR source): 2952, 1745, 1477, 1371, 1216, 1120, 731 cm^{-1}.; HRMS (ESI) *m*/*z*: calcd for $C_{18}H_{22}O_8SNa^+$ $[M + Na]^+$: 421.0933, found: 421.0934.

2.2.3 Methyl (methyl-2,3-di-*O*-acetyl-4-mercaptobenzyl-β-D-galactopyranosid) uronate (III). $R_f = 0.14$ (EtOAc : *n*-Hex = 1 : 3 v/v).; $[\alpha]_{589}^{25} = -60.7°$ ($c = 0.5$, $CHCl_3$).; ^1H NMR (300 MHz, $CDCl_3$, 297 K): $\delta = 7.31–7.20$ (m, 5H, Ar), 5.22 (dd, $J_1 = 10.2$ Hz, $J_2 = 7.8$ Hz, 1H, H_2), 5.08 (dd, $J_1 = 10.2$ Hz, $J_2 = 4.4$ Hz, 1H, H_3), 4.33–4.31 (m, 2H, H_1, H_5), 3.68–3.61 (m, 5H, OMe, CH_2Ph), 3.57 (dd, $J_1 = 4.4$ Hz, $J_2 = 2.0$ Hz, 1H, H_4), 3.52 (s, 3H, OMe), 2.05 (s, 3H, OAc), 1.96 (s, 3H, OAc) ppm.; ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 170.38, 169.44, 167.40, 137.91, 129.29, 128.73, 127.42, 102.23, 74.18, 72.94, 69.70, 56.99, 52.61, 46.78, 37.66, 20.89 ppm.; IR (ATR source): 2953, 1739, 1495, 1368, 1218, 1097, 731 cm^{-1}.; HRMS (ESI) *m*/*z*: calcd for $C_{19}H_{24}O_8SNa^+$ $[M + Na]^+$: 435.1192, found: 435.1190.

2.2.4 Methyl (methyl-2,3-di-*O*-acetyl-4-mercaptobenzyl-β-l-altropyranosid) uronate (IV). R_f = 0.50 (EtOAc : *n*-Hex = 1 : 3 v/v).; $[\alpha]_{589}^{25} = -56.6°$ (c = 0.5, $CHCl_3$).; ^1H NMR (300 MHz, $CDCl_3$, 297 K): $\delta = 7.32–7.25$ (m, 5H, Ar), 4.78–4.76 (m, 2H, H_2, H_3), 4.62 (d, $J = 0.5$ Hz, 1H, H_1), 4.55 (d, $J = 10.9$ Hz, 1H, H_5), 3.84 (s, 3H, OMe), 3.72 (d, $J = 1.4$ Hz, 2H, CH_2Ph), 3.37 (s, 3H, OMe), 3.19 (dd, $J_1 = 10.9$ Hz, $J_2 = 2.6$ Hz, 1H, H_4), 2.09 (s, 3H, OAc), 2.02 (s, 3H, OAc) ppm.; ^{13}C NMR (75 MHz, $CDCl_3$, 296 K): δ = 169.99, 169.93, 169.33, 137.30, 129.38, 128.69, 127.51, 98.47, 69.47, 68.85, 67.33, 56.13, 52.73, 40.98, 36.57, 20.97, 20.89 ppm.; IR (ATR source): 2952, 1745, 1602, 1495, 1218, 1093, 1025, 739 cm^{-1}.; HRMS (ESI) *m*/*z*: calcd for $C_{19}H_{24}O_8SNa^+$ $[M + Na]^+$: 435.1192, found: 435.1192.

2.3 General protocol for radical-mediated hydrothiolation reaction

To a solution of $\Delta^{4,5}$-unsaturated uronate derivate, **1β** (1 equiv.) in toluene at a final concentration of 0.2 M was added photoinitiators (5 equiv.) and BnSH (3 equiv.). The solution was deoxygenated and irradiated at ambient temperature for 1 hour. The addition of photoinitiators and irradiation was repeated three times more. Then, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography giving desired product. The isolated yield of desired compound was around 30%.

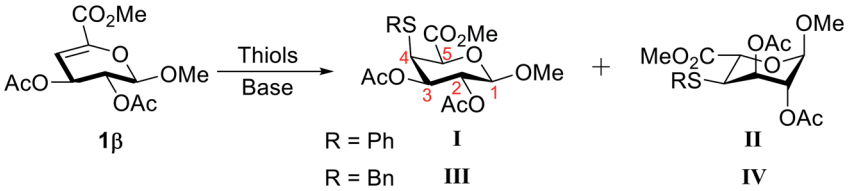
2.4 Compound V: methyl (methyl-2,3-di-*O*-acetyl-4-thiol-α-D-galactofuranosid) uronate

To a solution of **IV** (30.4 mg, 0.07 mmol) in 0.3 mL dry toluene was added $AlCl_3$ (34.8 mg, 0.3 mmole). The reaction was stirred at room temperature for 48 h. When the reaction was completed, it was quenched with cold demi water and the pH value was adjusted to 1 with 1 N $HCl_{(aq)}$. The aqueous layer was extracted with EtOAc three times. The organic layer was combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by flash column chromatography yielding desired products as yellow oil. $R_f = 0.29$ (EtOAc : *n*-Hex = 1 : 1.5 v/v).; ^1H NMR (300 MHz, $CDCl_3$, 298 K): 5.89 (dd, $J_1 = 9.1$ Hz, $J_2 = 6.5$ Hz, 1H, H_3), 5.19 (dd, $J_1 = 9.1$ Hz, $J_2 = 4.2$ Hz, 1H, H_2), 4.96 (d, $J = 4.2$ Hz, 1H, H_1), 4.45 (d, $J = 4.8$ Hz, 1H, H_5), 3.81 (s, 3H, OMe), 3.61 (dd, $J_1 = 6.4$ Hz, $J_2 = 4.9$ Hz, 1H, H_4), 3.31 (s, 3H, OMe), 2.09 (s, 3H, OAc), 2.08 (s, 3H, OAc) ppm.; ^{13}C NMR (75 MHz, $CDCl_3$, 302 K): 172.25, 170.59, 84.35, 78.71, 72.42, 56.48, 52.91, 48.37, 21.04, 20.91 ppm; IR (KBr): 3469, 2958, 1739, 1634, 1439, 1239, 1118, 912, 739 cm^{-1}.; HRMS (ESI) *m*/*z*: calcd for $C_{12}H_{18}O_8SNa^+$ $[M + Na]^+$: 345.0615, found: 345.0621.

3. Results and discussion

To investigate the feasibility of hydrothiolation reaction, $\Delta^{4,5}$-unsaturated methyl uronate **1β** was used as glycosyl donor and PhSH or BnSH were chosen as the model thiol reagents. Initially, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was applied as a base to mediate the thiol-Michael addition. The reaction mixture was stirred at 80 °C for 6 hours yielding two PhSH attached products, namely **I** and **II**, in a lower yield, and the ratio of these two products is 1.8 : 1 (Table 1, entry 1). The structures of compounds **I** and **II** were characterized by detailed 1D and 2D NMR spectroscopy (see ESI†). The NOESY spectrum (Fig. S1A†) of **I** shows a strong NOE interaction between the H-5, H-1, and H-3, which indicates that these protons are located on the axial positions of the six-membered ring and confirms that the product **I** in the $^4C_1$ conformation. In contrast, a NOE effect was observed between the H-5 and H-2 of **II**, which indicated that the H-5 and H-2 of **II** were spatially near each other and showed that the product **II** in the $^1C_4$ conformation (Fig. S1B†). Encouraged by this initial result, various bases were subsequently surveyed to optimize the reaction condition (Table 1, entries 2–5). 4-Dimethylaminopyridine (DMAP) resulted in the highest yield among these bases, although the ratio of these two PhSH attached products was slightly decrease compared to the result from the use of DBU. To improve the stereoselectivity of the C-5 position, the reactions were carried out at different temperatures (Table 1, entries 5–7). The stereoselective at the C-

Table 1 Optimization of base-mediated thiol-Michael addition of **1β** with thiols[a]



Entry	Base	Solvent	Thiol (equiv.)	Temp.	Time	Result[b]
1	DBU	CH_3CN	PhSH (10)	80 °C	6 h	**I**/**II** (28%, 1.8 : 1)
2	TEA	CH_3CN	PhSH (10)	80 °C	6 h	**I**/**II** (52%, 1.5 : 1)
3	Quinine	CH_3CN	PhSH (10)	80 °C	6 h	**I**/**II** (40%, 1.3 : 1)
4	DBACO	CH_3CN	PhSH (10)	80 °C	6 h	**I**/**II** (45%, 0.6 : 1)
5[c]	DMAP	CH_3CN	PhSH (10)	80 °C	6 h	**I**/**II** (65%, 1.3 : 1)
6	DMAP	CH_3CN	PhSH (10)	60 °C	6 h	**I**/**II** (36%, 1.5 : 1)
7	DMAP	CH_3CN	PhSH (10)	40 °C	18 h	**I**/**II** (42%, 1.8 : 1)
8	DMAP	CH_3CN	PhSH (10)	60 °C	18 h	**I**/**II** (72%, 1.6 : 1)
9	DMAP	CH_3CN	PhSH (5)	60 °C	18 h	**I**/**II** (58%, 1 : 1)
10	DMAP	CH_3CN	PhSH (1.5)	60 °C	18 h	**I**/**II** (N.D, N.D.)
11	DMAP	THF	PhSH (10)	60 °C	18 h	**I**/**II** (N.D, N.D.)
12	DMAP	Toluene	PhSH (10)	60 °C	18 h	**I**/**II** (39%, 1.2 : 1)
13	DMAP	$CHCl_3$	PhSH (10)	60 °C	18 h	**I**/**II** (62%, 0.7 : 1)
13	DMAP	CH_3CN	BnSH (10)	80 °C	12 h	**III**/**IV** (60%, 17 : 1)

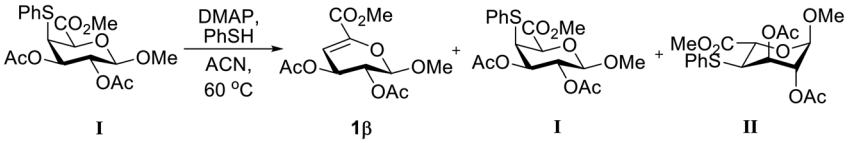
[a] General procedure: **1β** (1 equiv.) and bases (1 equiv.) were dissolved in the indicated solvent and then the thiols were added under various temperatures. After stirring, the reaction mixture was worked up, concentrated under reduced pressure, and purified by flash column chromatography. [b] Yield percentage and the ratio of products were determined by HPLC analysis. [c] When the reaction time was elongated to 12 h, the yield was up to 86%.; N.D. = not detected.

5 position was somewhat improved at a lower temperature. Metallic Lewis acids and alcohols with steric hindrance were also have been tried to ameliorate the stereoselectivity (Table S1†),[22,23] however, the ratio of these two thiol attached products remains around 1 : 1. Owing to air oxidation of thiols to form disulfide, an excess amount of PhSH was required to obtain a decent yield (Table 1, entries 8–10). To determine whether any other solvent could be suitable for this methodology, a survey of reaction media was conducted. The reaction was performed in different solvents, including acetonitrile, toluene, chloroform, and tetrahydrofuran. The results revealed that acetonitrile was the optimal solvent for this reaction (Table 1, entry 8). No reaction occurred when tetrahydrofuran was employed (Table 1, entry 11) and both the reactivity and selectivity were decreased when toluene or chloroform were used (Table 1, entries 12 and 13). Next, BnSH as a nucleophile based on the best condition was also tested in this system. Surprisingly, the ratio of two BnSH adducts is increased to 17 : 1 with a reasonable yield (Table 1, entry 14). It is worth noticing that **1β** was not fully consumed under these reaction conditions even with elongated reaction time and that could be recovered after purification.

In a comparison with BnSH, PhSH has a lower pK_a value, as a consequence, a retro thiol-Michael addition may more likely to occur resulting base-catalyzed equilibration between **I** and **II**. To investigate this hypothesis, compound **I** was treated with DMAP under the best-optimized condition. After few hours, an appreciable amount of elimination product, **1β**, was observed (Table 2, entries 1–3). Upon addition of PhSH, the rate of elimination was increased and led to equilibration with **1β**, **I**, and **II** (Table 2, entries 4–6). A similar outcome was obtained, when **III** was treated with DMAP and BnSH. However, the rate of retro thiol-Michael addition was slower owing to the higher pK_a value of BnSH (Table S2†). These results confirmed the occurrence of retro thiol-Michael addition under alkaline conditions.

Thereafter, a radical initiated hydrothiolation reaction was surveyed and BnSH was used as an example. Although a thiol–ene radical reaction could be generated without any initiator, azobis(isobutyronitrile) (AIBN), dibenzoyl peroxide (DPO), and 2,2-dimethoxy-2-phenylacetophenone (DPAP) were used here to promote the efficiency of this reaction. At the beginning, thermally activated initiators, AIBN and DPO, were utilized (Table 3, entries 1 and 2). However, there was no adduct was observed under these reaction conditions, and the starting material was recovered even excessive amount of thermal initiators and BnSH were applied. Then, the reaction was carried out with DPAP as photoinitiator in toluene with UVA lamp at 365 nm. Equivalent amount of BnSH and a catalytic amount of DPAP were initially utilized, however, only a trace amount of product was obtained (Table 3, entry 3). By contrast, disulfide-linked BnSH and incomplete conversion of the starting **1β** were indicated by TLC. To improve the yield, the reaction time was prolonged and an excess amount of DPAP and BnSH were used (Table 3, entry 4). Under this condition, the desired adduct was obtained in 21% yield. Nevertheless, the further increase

Table 2 Retro thiol-Michael addition resulted in the equilibration between **1β**, I, and II



I **1β** I II

Entry	Thiol (eq.)	Time	Result[a] (%)
1	—	1 h	**I** (100)
2	—	3 h	**1β** + **I** (1 : 99)
3	—	12 h	**1β** + **I** (5 : 95)
4	PhSH (10)	1 h	**1β** + **I** (14 : 86)
5	PhSH (10)	3 h	**1β** + **I** + **II** (25 : 74 : 1)
6	PhSH (10)	12 h	**1β** + **I** + **II** (41 : 53 : 6)

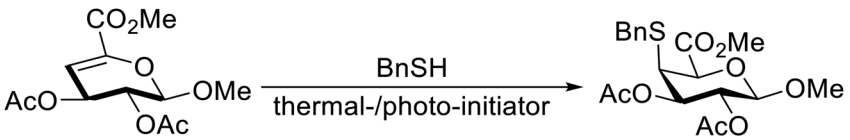
[a] The ratio of products was determined by HPLC analysis.

amount of BnSH and changing solvent system did not be able to improve the yield of this reaction (Table 3, entries 5 and 6). The low conversion yield might be attributed by the electron-withdrawing capability of COOMe that affects the electron density of the double bonds decreasing the reactivity of this reaction system.[24] Besides, internal alkenes are significantly less reactive towards radical hydrothiolation in a comparison with terminal alkenes[25] and a reversible equilibrium between thiyl radical and 4,5-disubstituted ene causing the low yield.[26] The position of thiol attached carbon (regioselectivity) and the conformation of adduct were confirmed by fully assigned 1-D and 2-D NMR spectra.

According to the results of alkaline/radical-mediated hydrothiolation reactions, plausible mechanisms were proposed and described in Fig. 2. Unsaturated uronic acid and its derivatives are mostly represented by half-chair form.[10,27,28] However, $^{1}H_{2}$ conformer is less stable than $^{2}H_{1}$ due to the steric hindrance between the anomeric methoxyl group and the acetate at the C-3 position. The *exo*-face attachment at the C-4 position yields a chair-like intermediate, but the *endo*-face attack gives a higher energy twist-boat-like intermediate. As a consequence, the thiol groups were attached to unsaturated uronate with axial-selectivity at the C-4 position. The following protonation of adducts at the C-5 position provides two different final products. These two products can be converted to each other *via* retro thiol-Michael addition (Fig. 2A). For radical-mediated reaction, photo-irradiative generated thiyl-radical was adding from the *exo*-face of **1β** and the subsequent hydrogen abstraction by the C-5 radical of the substrate took place from the axial-position resulting *S*-linkage product **III** (Fig. 2B).

Owing to the low yield of photo-irradiated hydrothiolation reaction, we following focused on the base-mediated approach for investigating the substrate scope between unsaturated methyl uronate **1β** with various thiol partners. Unfortunately,

Table 3 Optimization of $\Delta^{4,5}$-unsaturated uronate derivate **1β** with BnSH under radical-mediated hydrothiolation reaction



1β **III**

Entry	Initiator	Solvent	BnSH (equiv.)	Temp.	Time	Result[c]
1[a]	AIBN, Δ	Toluene	3	82 °C	8 h	N.R.
2[a]	DPO, Δ	Toluene	3	70 °C	8 h	N.R.
3[b]	DPAP, *hν*	Toluene	1	r.t.	4 h	Trace
4[b]	DPAP, *hν*	Toluene	3	r.t.	4 h	**III** (21%)
5[b]	DPAP, *hν*	Toluene	5	r.t.	4 h	**III** (18%)
6[b]	DPAP, *hν*	Toluene : MeOH (5 : 1)	3	r.t.	4 h	**III** (16%)

[a] Method A: the reaction was carried out with thermal initiators (10 equiv.) in a sealed tube and was heated in an oil bath. [b] Method B: the reactions were carried out by irradiation at λ_{max} 365 nm UVA lamp (8 W) for 1 × 4 h in the presence of DPAP (4 × 0.1 equiv.). [c] The yield is isolated yield. N.R. = no reaction and starting material was recovered.

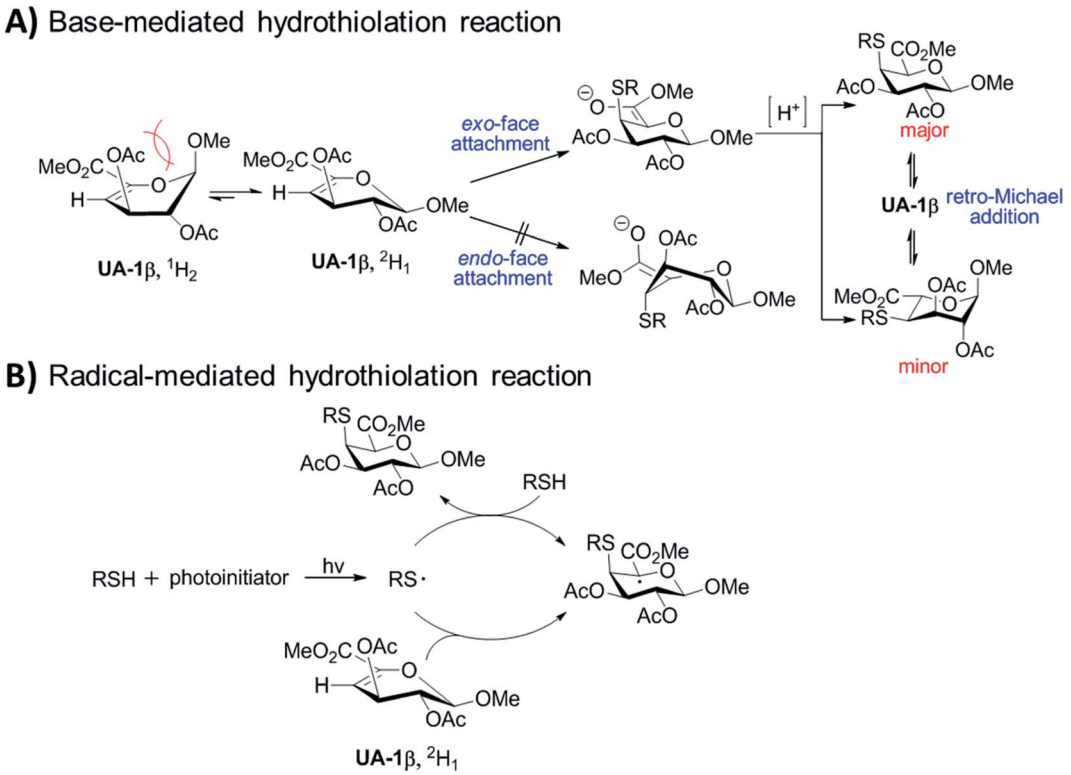
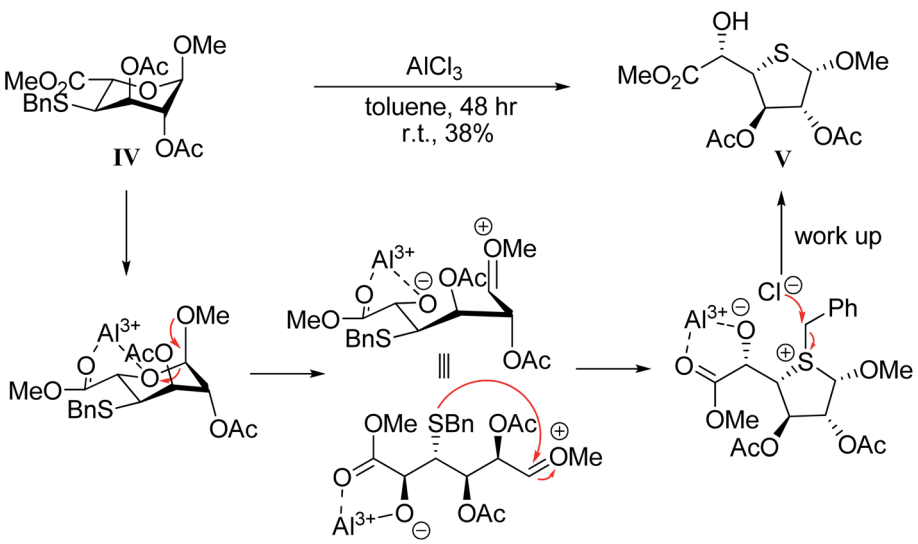


Fig. 2 Proposed mechanism of base-mediated (A) and radical-mediated (B) hydrothiolation reactions.

only a trace amount of adducts were observed either use a thio-sugar or a cysteine derivative. The adducts were difficult to be isolated due to the low conversion yield even after a prolonged reaction time (data not shown). The low conversion yield could be caused by the steric hindrance at the C-3 position. In this context, we change our strategy to prepared *S*-linked glycosides. The plan was to use 4-thiol uronate derivatives to attach glycosyl bromide to make *S*-linked disaccharide. As a consequence, the thiolbenzyl functionalized **IV** was de-protected using aluminum chloride.[29] Unexpectedly, α-furanosidic form of 4-thiol-uronate was obtained. During the reaction, aluminum(III) catalyzed the six-member ring opening. Subsequently, the sulfur was attached to the anomeric carbonium ion generating a sulfonium intermediate with a five-member ring molecular structure. After workup, thiol-furanoside **V** was obtained (Scheme 1). To the best of our knowledge, the thiol-furanoside **V** was synthesized for the first time.



Scheme 1 The use of $AlCl_3$ for the deprotection of *S*-linked uronate **IV**.

4. Conclusions

In summary, both base- and radical-mediated hydrothiolation reactions were applied for the synthesis of *S*-linked uronate derivatives, while the radical-mediated reaction was inefficient due to the electron-withdrawing group on ethylene group. For the alkaline approach, PhSH or BnSH as nucleophiles could regioselectively and stereoselectively attach to the C-4 position of unsaturated uronate. However, a poor stereoselectivity at the C-5 position was observed owing to retro thiol-Michael addition. When the use of $AlCl_3$ to remove the benzyl protecting group, 4-thiol-furanosidic uronate was synthesized for the first time.

Conflicts of interest

There are no conflicts to declare.

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