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Structure and temperature controlled synthesis of novel thiazolidin-4-one derivatives bearing an azasugar

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ABSTRACT

Novel thiazolidin-4-one linked pseudo-aza-disaccharides and thiazolidin-4-ones containing *C*-pseudo-aza-nucleosides were synthesized via a one-pot three component reaction. The former was synthesized stereoselectively by the tandem Staudinger/aza-Wittig/cyclization reaction of azasugar aldehyde **1**, an azidosugar, and mercaptoacetic acid. The reaction was structure and temperature controlled, and could be performed stereospecifically under 40 °C. It was the first report of a stereospecific synthesis of thiazolidin-4-one linked derivatives. However, these derivatives were synthesized with low stereoselectivity by involving the condensation reaction of azasugar aldehyde **1**, aniline, and mercaptoacetic acid.

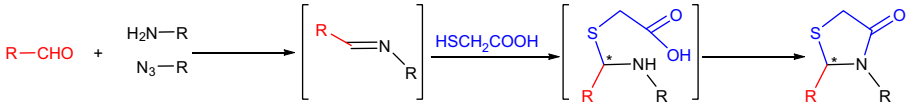
1. Introduction

The thiazolidin-4-one ring is a core substructure in various synthetic pharmaceuticals, which is associated with diverse biological activities such as antibacterial, anti-fungal, anti-cancer, antiviral, anti-inflammatory and analgesic, and calcium antagonistic.[1,2] Recently, thiazolidin-4-one linked pseudodisaccharides and thiazolidin-4-one containing *C*-pseudonucleosides have been demonstrated to possess strong immunostimulatory activities.[3,4] Generally, thiazolidin-4-one derivatives have been synthesized in two ways; one is the one-pot three component condensation from an amine, a carbonyl compound, and a mercaptoacetic acid via an intermediate imine,[5–8] and the other is the tandem Staudinger[9]/aza-Wittig[10]/cyclization reaction employing an azide compound instead of amine (Scheme 1).[3,11] However, both protocols were carried out with almost no stereoselectivity and commonly afforded a pair of the stereoisomers. To the best of our knowledge, the only example of stereospecific formation of the thiazolidin-4-one ring was found in the synthesis of thiazolidin-4-one fused bicyclic azasugar analogues.[12] In a continuation of our studies on bioactive thiazolidin-4-one derivatives containing a sugar moiety,[13] we herein report a structure and temperature controlled synthesis of thiazolidin-4-one derivatives containing an azasugar. Novel thiazolidin-4-one linked pseudo-aza-disaccharides were first synthesized stereospecifically by the Staudinger/aza-Wittig/cyclization reaction starting from azasugar aldehyde **1**, azidosugar **2a**–**d**, and mercaptoacetic acid. In addition, thiazolidin-4-one containing *C*-pseudo-aza-nucleosides were synthesized from azasugar aldehyde **1**, aniline **2e**–**f**, and mercaptoacetic acid.

2. Results and discussion

According to the reported procedures,[14] the requisite azasugar aldehyde **1** and the azido azasugar **2c** can be readily prepared from D-mannose, while azidosugars **2a** and **2b** can be synthesized from D-glucose and D-ribose, respectively. As shown in Scheme 2, the azido azasugar **2d** was synthesized from *N*-TFA-protected azido azasugar **5** via the deprotection of the TFA and Bz groups, followed by *N*-Boc protection.

Based on our previous report,[3] the synthesis of thiazolidin-4-one linked pseudo-aza-disaccharides **3a** and **3a′** was carried out by the tandem Staudinger/aza-Wittig reaction of azasugar aldehyde **1** and



Scheme 1. The one-pot three component reactions for the synthesis of thiazolidin-4-one.

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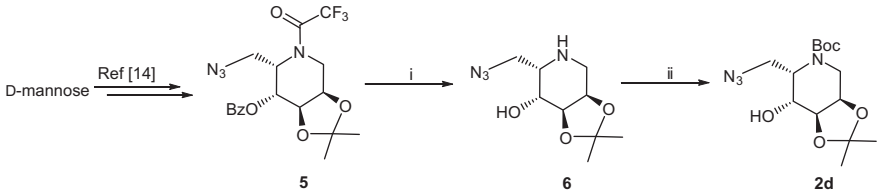


Scheme 2. The synthesis of the six-membered azasugar azide **2d**. Reagents and conditions: (i) K_2CO_3, MeOH, 40 °C, 3 h, 95%; (ii) Boc_2O, Et_3N, DCM, MeOH, 2 h, 80%.

azidosugar **2a** stirring with triphenylphosphine (Ph_3P) to generate the imine intermediate via an iminophosphorane, followed by in situ condensation with mercaptoacetic acid, as shown in Scheme 3. Temperature had a significant effect on both the reaction yield and the reaction stereoselectivity as shown in Table 1. The synthesis was studied first at room temperature, but no product was formed after 12 h. However, when the reaction was carried out at 40 °C, the reaction proceeded stereospecifically and afforded a single product **3a** in a good yield of 70%. When the temperature was increased to 60 °C, the reaction produced the corresponding diastereomeric thiazolidin-4-one derivatives **3a** (more polar and a majority) and **3a′** (less polar and a minority) with a high stereoselective ratio of 10:1. As the temperature increased to 80 °C, the ratio of **3a** and **3a′** decreased to 6:1 with a total yield of 57%, and the reaction provided the diastereomeric products in a total yield of 48% with an isomeric ratio of 6:1 when the reaction was carried out at 120 °C.

Under the same conditions as described in Table 1 entry 2, the one pot reaction of azasugar aldehyde **1** and other azido sugars **2b–d** was carried out at 40 °C and stereospecifically afforded the single stereoisomers **3b–d** in good yields of 66–72%, respectively (Scheme 4). To the best of our knowledge, this is the first example of the stereospecific synthesis of thiazolidin-4-one derivatives by a one-pot three component reaction.

Mechanically, the stereochemistry in constructing thiazolidin-4-one depends on the nucleophilic condensation of imine (C=N) and $HSCH_2COOH$. In order to investigate the main structural effects on the reaction selectivity, we carried out the reaction using azasugar aldehyde **1** with aniline **2e** and 4-chloro aniline **2f** instead of the azido sugars at 40 °C (Scheme 5). However, both reactions afforded the diastereomeric products of the thiazolidin-4-one containing *C*-pseudo-aza-nucleosides **3e–f** (more polar and a majority) and **3e′–f′** (less polar and a minority) in a ratio of 2:1, and so exhibited low stereoselectivity. Considering the previous results[3] in which the synthesis of the thiazolidin-4-one linked pseudodisaccharides by the tandem reaction from a sugar aldehyde with azidosugars **2a** or **2b** proceeded with very low stereoselectivity, we postulate that the highly stereoselective synthesis shown in Scheme 3 would be likely due to the synergistic hindrance effects of the two sugar groups and the *N*-Boc group.

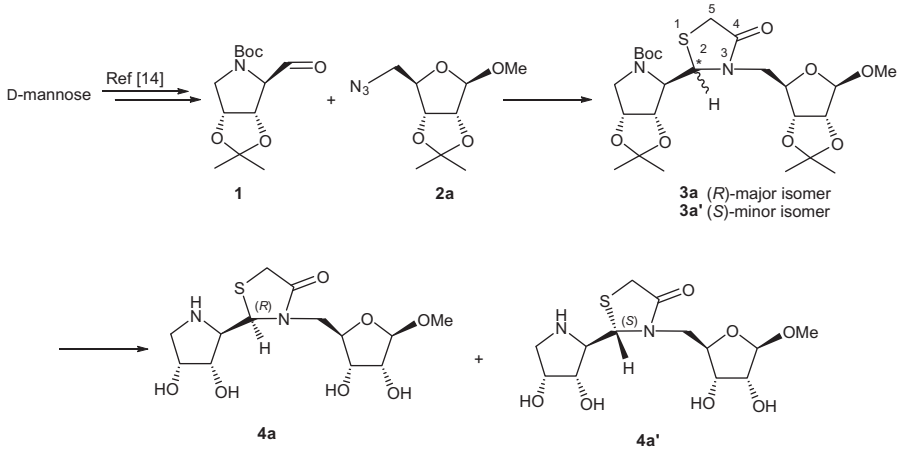
Table 1
Exploratory studies of the tandem reaction using **1** and **2a**[a]

Entry	Temp (°C)	Ratio of **3a**:**3a′**[b]	Total yield of **3a** and **3a′**[c]
1	rt	—[d]	—
2	40	1:0	70%
3	60	10:1	65%
4	80	6:1	57%
5	100	6:1	50%
6	120	6:1	48%

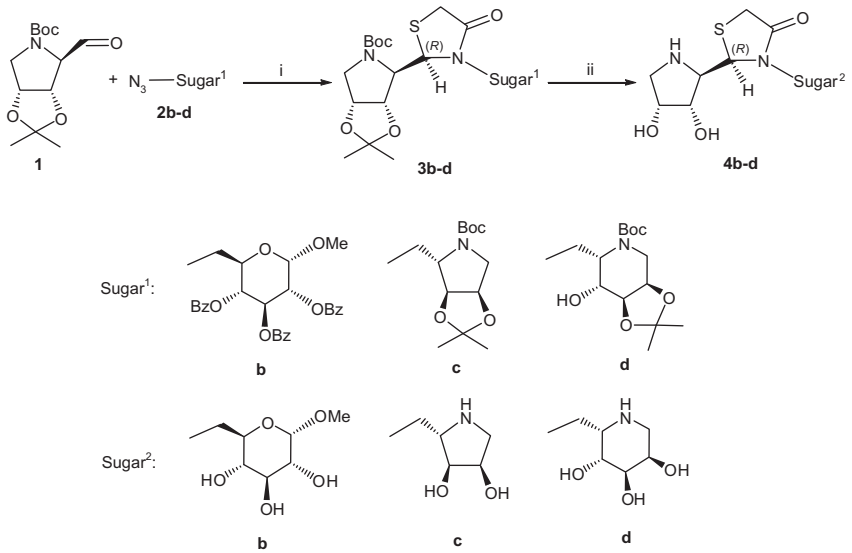
[a] The ratio of reactants: **1**:**2a**:Ph_3P:$HSCH_2COOH$ = 1:1:1.1:2. Compounds **1a**, Ph_3P, and **2a** were first stirred for 30 min in toluene, then mercaptoacetic acid was added and stirred for another 12 h until the starting materials disappeared by TLC.
[b] Determined by ^1H NMR.
[c] Isolated yield.
[d] No products were detected after 12 h.

Thus, the bulky chiral sugars might cause a dominant attack of the sulfur atom onto the imine from one side and generate one isomer as the predominant product at 40 °C. As the reaction temperature increased, the molecular movement was accelerated, lowering the reaction stereoselectivity. In the cases of **2e** and **2f**, the planar phenyl group diminished the hindrance effect, which led to a nearly equal attack of the sulfur atom from both sides of the imine and afforded the diastereomers with low stereoselectivity.

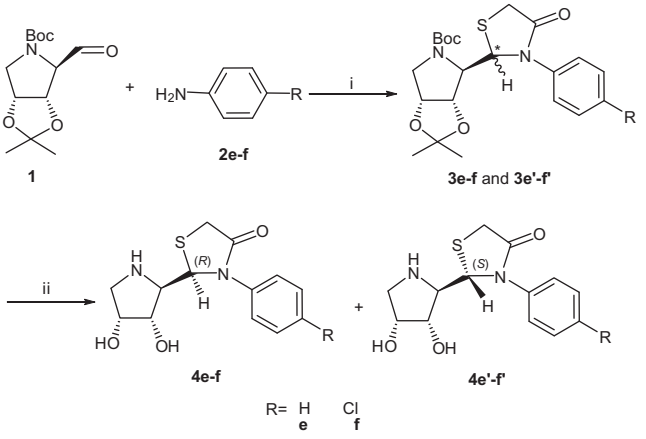
The further deprotection of **3** could effectively produce the corresponding products **4** in good yields. The structures of the new compounds were determined according to analyses of their ^1H NMR, ^{13}C NMR, and HR ESI MS spectra. The structure of **4e′** was confirmed by single-crystal X-ray analysis (Fig. 1),[15] in which the



Scheme 3.



Scheme 4. The stereospecific synthesis of thiazolidin-4-one linked pseudo-aza-disaccharides. Reagents and conditions: (i) PPh_3, $HSCH_2COOH$, 12 h, 66–72%; (ii) for **4c–d**: 90% CF_3COOH/H_2O, 1 h, 80%; for **4b**: (a) MeOH/MeONa, 1 h, (b) 90% CF_3COOH/H_2O, 1 h, 50%.



Scheme 5. The synthesis of the thiazolidin-4-one containing *C*-pseudo-aza-nucleosides. Reagents and conditions: (i) $HSCH_2COOH$, DCC, DMAP, 12 h, total yields 62–70%; (ii) 90% CF_3COOH/H_2O, 1 h, 85–90%.

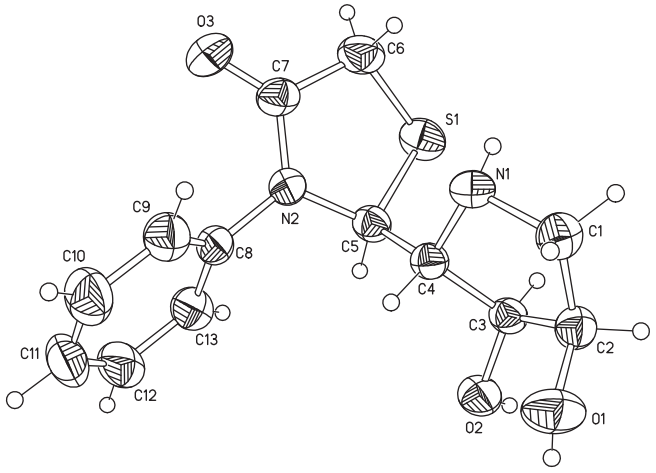


Figure 1. X-ray crystallographic structure of **4e′**.

Table 2
The ^1H NMR signal (δ = ppm) of H-2 in compounds **4**

Compounds	4a	4b	4c	4d	4e	4f
$\delta_{H\text{-}2}$ (*R* form)	5.26	5.23	5.04	5.03	5.32	5.48
$\delta_{H\text{-}2}$ (*S* form)	5.38 **4a′**				5.49 **4e′**	5.50 **4f′**

new generated chiral carbon (C-2) had the (*S*)-configuration. Therefore, its diastereomer **4e** should have an (*R*)-configuration at C-2. In our previous studies,[3,11] we have found an important correlation between the stereochemistry of C-2, the molecular polarity and the chemical shift of H-2. Based on the crystallographic structure of **4e′** and with the comparison of the chemical shifts of H-2 summarized in Table 2, the structures of **4a**, **4a′**, **4f** and **4f′** could be tentatively determined. Thus, similar to the observations in the cases of **4e** and **4e′**, compounds **4a** and **4f** have more polarity and higher up-field chemical shifts of H-2 than those of their isomers **4a′** and **4f′** (Table 2), implying that their C-2s in **4a** and **4f** have an (*R*)-configuration. Accordingly, compounds **4b–d** and **3a–f** should have an (*R*)-configuration, and compounds **3a′**, **3e′–f′** should possess an (*S*)-configuration at C-2.

3. Conclusion

In conclusion, novel thiazolidin-4-one linked pseudo-aza-disaccharides **4a–d** were synthesized stereoselectively by a Staudinger/aza-Wittig/cyclization reaction. The reaction stereoselectivity could be controlled by the structure of the reactants (*N*-Boc protected azasuger aldehyde and azido sugars), while temperature also had a significant impact on the reaction. The present findings may provide an important reference for the asymmetry synthesis of thiazolidin-4-ones. The examination of the immunostimulating activity of these compounds is currently underway in our laboratory.

4. Experimental section

4.1. General methods

Melting points were measured on an SGW X-4 micro melting point apparatus. Optical rotations were determined on an SGW-1

automatic polarimeter. ^{1}H NMR and ^{13}C NMR spectra were measured on a Brucker advance II 600 FT-NMR spectrometer using tetramethylsilane (Me_4Si) as the internal standard. High-resolution mass spectra (HRMS) were carried out on a FTICR-MS (Ionspec 7.0 T) mass spectrometer with electrospray ionization (ESI). X-ray crystallographic measurements were made on a Bruker SMART CCD diffractometer. Thin-layer chromatography (TLC) was performed on precoated plates (Qingdao GF254) with detection by UV light or with phosphomolybdic acid in EtOH–H_2O followed by heating. Column chromatography was performed using SiO_2 gel (Qingdao 300–400 mesh).

4.2. Synthesis of compound 6

Compound **5** (5.7 g, 13.3 mmol) was dissolved in 270 mL of anhydrous MeOH, after which anhydrous K_2CO_3 (5 equiv) was added. After continued stirring for 3 h at 40 °C under a nitrogen atmosphere, the mixture was neutralized with dilute HCl and concentrated and extracted with (100 mL × 3) of ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give a crude product, which was purified using column chromatography (petroleum ether:ethyl acetate V/V 4:1) to furnish compound **6**.

4.2.1. (3a*R*,6*S*,7*R*,7a*S*)-6-(Azidomethyl)-2,2-dimethylhexahydro-[1,3]dioxolo[4,5-*c*]pyridin-7-ol 6

White solid, yield 95%, mp 143.0–144.0 °C, $[\alpha]_D^{25} = +32.6$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ_H: 1.38 (3H, s, CH_3), 1.52 (3H, s, CH_3), 2.72 (1H, dd, *J* = 12.6 Hz, 4.8 Hz, CH), 3.08, 3.20 (2H, CH_2), 3.43, 3.56 (2H, CH_2), 3.92 (1H, t, *J* = 2.4 Hz, CH), 4.22 (1H, q, *J* = 2.4 Hz, CH), 4.28–4.31 (1H, m, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 26.1, 28.0, 47.9, 52.7, 54.6, 70.8, 76.3, 77.2, 109.4; HRMS (ESI): Calcd for $C_9H_{17}N_4O_3$ ($[M+H]^+$): 229.1304. Found: 229.1301.

4.3. Synthesis of compound 2d

A mixture of compound **6** (2.9 g, 12.7 mmol), Boc_2O (2 equiv), and TEA (3 equiv) in anhydrous MeOH (100 mL) was stirred at room temperature for 2 h under a nitrogen atmosphere, then concentrated under reduced pressure to give a crude product, which was purified using column chromatography (petroleum ether:-ethyl acetate V/V 10:1) to give **2d**.

4.3.1. (3a*R*,6*S*,7*R*,7a*S*)-*tert*-Butyl 6-(azidomethyl)-7-hydroxy-2,2-di methyltetrahydro-[1,3]dioxolo[4,5-*c*]pyridine-5(6*H*)-carboxylate 2d

White solid, yield 80%, mp 100.1–102.0 °C, $[\alpha]_D^{25} = +28.4$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ_H: 1.32 (3H, s, CH_3), 1.38–1.48 (12H, m, 4 CH_3), 3.24, 3.37 (1H, d, *J* = 14.4 Hz, CH), 3.54–3.70 (2H, m, CH_2), 4.01–4.34 (5H, CH_2, 3CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 24.2, 26.4, 28.3, 40.9, 42.2, 49.3, 49.7, 51.0, 51.8, 66.0, 66.8, 72.5, 72.6, 73.6, 73.7, 80.2, 80.4, 109.4; HRMS (ESI): Calcd for $C_{14}H_{24}N_4O_5Na$ ($[M+Na]^+$): 351.1644. Found: 351.1638.

4.4. General procedure for the synthesis of compounds 3a–d and 3a′

Azidosugar **2a** (1.0 g, 3.7 mmol), Ph_3P (1.1 equiv), and azasugar aldehyde **1** (1.0 equiv) were dissolved in 200 mL of anhydrous toluene, and the mixture was stirred in 40 °C for 30 min under a nitrogen atmosphere. Next, mercapto acetic acid (2.0 equiv) was added. After continued stirring for 12 h at 40 °C (80 °C for **3a** and **3a′**), the mixture was neutralized with aqueous $NaHCO_3$ and extracted with (100 mL × 3) of ethyl acetate; the organic layer was washed successively with water (50 mL × 2) and saturated brine (50 mL × 2), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give a crude product, which was purified using column chromatography (petroleum ether:ethyl acetate V/V 4:1) to afford **3a**. Under the same conditions, compounds **3b**–**d** were obtained.

4.4.1. (3a*S*,4*R*,6a*R*)-*tert*-Butyl 4-((*R*)-3-(((3a*R*,4*R*,6*R*,6a*R*)-6-methoxy-2,2-dimethyl-tetrahyd-rofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)-4-oxothiazolidin-2-yl)-2,2-dimethyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate 3a

Pale yellow syrup, yield 49%; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H: 1.25–1.45 (21H, m, 7CH_3), 3.16 (1H, dd, *J* = 13.8 Hz, 4.8 Hz, CH_2), 3.28 (3H, s, –OCH_3), 3.55–3.69 (3H, m, CH_2, CH), 3.95 (1H, d, *J* = 12.6 Hz, CH), 4.07 (1H, dd, *J* = 13.8 Hz, 10.8 Hz, CH), 4.34 (1H, d, *J* = 3.0 Hz, CH), 4.49 (1H, d, *J* = 6.0 Hz, CH), 4.51–4.61 (2H, m, CH_2), 4.66–4.69 (1H, m, CH), 4.79 (1H, t, *J* = 5.4 Hz, CH), 4.97 (1H, s, CH), 5.28 (1H, s, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 24.7, 26.2, 27.1, 28.5, 31.9, 46.7, 53.7, 55.5, 60.9, 66.2, 79.0, 79.9, 80.7, 81.3, 81.9, 82.8, 85.4, 110.1, 112.6, 153.5, 171.2; HRMS (ESI): Calcd for $C_{24}H_{38}N_2O_9SNa$ ($[M+Na]^+$): 553.2195. Found: 553.2187.

4.4.2. (3a*S*,4*R*,6a*R*)-*tert*-Butyl 4-((*S*)-3-(((3a*R*,4*R*,6*R*,6a*R*)-6-methoxy-2,2-dimethyl-tetrahydr-ofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)-4-oxothiazolidin-2-yl)-2,2-dimethyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate 3a′

Pale yellow syrup, yield 8%; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H: 1.30–1.46 (21H, m, 7CH_3), 3.07–3.77 (7H, m, 2CH_2, –OCH_3), 3.91, 4.17 (1H, d, *J* = 12.6 Hz, CH), 3.96–4.08 (1H, m, CH), 4.26–4.36 (1H, m, CH), 4.44 (1H, d, *J* = 6.0 Hz, CH), 4.63–4.68 (3H, CH_2, CH), 4.86–4.89 (1H, m, CH), 4.96, 5.13 (1H, CH), 4.98 (1H, s, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 24.9, 25.0, 26.5, 28.3, 31.9, 46.5, 55.9, 63.9, 65.2, 79.9, 80.5, 80.6, 82.4, 82.8, 85.8, 110.7, 112.6, 155.1, 170.5; HRMS (ESI): Calcd for $C_{24}H_{38}N_2O_9SNa$ ($[M+Na]^+$): 553.2195. Found: 553.2198.

4.4.3. (2*R*,3*R*,4*S*,5*R*,6*S*)-2-(((*R*)-2-((3a*S*,4*R*,6a*R*)-5-(*tert*-Butoxy carbonyl)-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrr-ol-4-yl)-4-oxothiazolidin-3-yl)methyl)-6-methoxytetra hydro-2*H*-pyran-3,4,5-triyl tribenzoate 3b

Pale yellow syrup, yield 72%; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H: 1.25–1.62 (15H, 5CH_3), 3.47–3.77 (8H, m, 2CH_2, –OCH_3, CH), 3.96, 4.08 (1H, CH), 4.46–4.57 (2H, m, CH_2), 4.62–4.65 (1H, m, CH), 4.78–4.80 (1H, m, CH), 5.07–5.29 (3H, 3CH), 5.41–5.48 (1H, m, CH), 6.10–6.17 (1H, m, CH), 7.28–8.00 (15H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 24.9, 26.7, 28.2, 28.4, 29.7, 31.7, 45.0, 55.6, 61.4, 65.6, 70.1, 70.7, 71.9, 79.2, 80.2, 81.1, 96.6, 96.9, 111.8, 128.2, 128.4, 128.5, 128.9, 129.1, 129.2, 129.6, 129.9, 131.9, 132.0, 133.0, 133.2, 153.6, 154.1, 165.4, 165.7, 171.1, 171.5; HRMS (ESI): Calcd for $C_{43}H_{48}N_2O_{13}SNa$ ($[M+Na]^+$): 855.2774. Found: 855.2771.

4.4.4. (3a*S*,4*S*,6a*R*)-*tert*-Butyl 4-(((*R*)-2-((3a*S*,4*R*,6a*R*)-5-(*tert*-butoxycarbonyl)-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo [4,5-*c*]pyrrol-4-yl)-4-oxothiazolidin-3-yl)methyl)-2,2-dimethyl dihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate 3c

Pale yellow syrup, yield 70%; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H: 1.29–1.53 (30H, 10CH_3), 3.10, 3.40 (2H, CH_2), 3.47–3.91 (5H, 2CH_2, CH), 4.04–4.09 (1H, m, CH), 4.27–4.31 (1H, m, CH), 4.38–4.80 (5H, m, CH), 5.11, 5.24, 5.33 (1H, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 24.6, 25.6, 27.6, 28.3, 31.7, 41.9, 50.7, 53.7, 60.3, 65.5, 79.6, 80.6, 81.2, 81.8, 112.1, 112.3, 153.6, 154.3, 171.5; HRMS (ESI): Calcd for $C_{28}H_{45}N_3O_9SNa$ ($[M+Na]^+$): 622.2774. Found: 622.2775.

4.4.5. (3a*R*,6*S*,7*R*,7a*S*)-*tert*-Butyl 6-6-(((*S*)-2-((3a*S*,4*R*,6a*R*)-5-(*tert*-butoxycarbonyl)-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrol-4-yl)-4-oxothiazolidin-3-yl)methyl)-7-hydroxy-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-*c*]pyridine-5(6*H*)-carboxylate 3d

Pale yellow syrup, yield 66%; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H: 1.31–1.51 (30H, 10CH_3), 3.38 (2H, d, J = 9.6 Hz, CH_2), 3.52–3.58 (2H, m, CH_2), 3.62 (1H, d, J = 9.6 Hz, CH), 3.89–3.95 (3H, m, CH, CH_2), 4.10 (1H, d, J = 13.2 Hz, CH), 4.28 (1H, d, J = 7.8 Hz, CH), 4.46 (1H, dd, J = 7.8 Hz, 3.6 Hz, CH), 4.55 (1H, d, J = 13.2 Hz, CH), 4.67–4.74 (3H, m, 3CH), 5.04, 5.22 (1H, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 24.0, 25.4, 26.1, 27.1, 28.2, 31.3, 41.8, 49.6, 51.8, 61.1, 63.8, 66.5, 72.7, 72.8, 78.9, 79.7, 80.9, 81.6, 109.2, 112.2, 154.2, 155.5, 173.5; HRMS (ESI): Calcd for $C_{29}H_{47}N_3O_{10}SNa$ ([M+Na]$^+$): 652.2879. Found: 652.2882.

4.5. General procedure for the synthesis of compounds 3e–f and 3e′–f′

Aniline **2e** or chloroaniline **2f** (1 mL) and sugar aldehyde **1** (1.2 equiv) were dissolved in 30 mL of anhydrous toluene. The mixture was then stirred in 40 °C for 1 h under a nitrogen atmosphere. Next, mercapto acetic acid (2.0 equiv), DCC (1.2 equiv), and DMAP (0.2 equiv) were added. After continued stirring for 12 h, the mixture was filtered and washed by ether, neutralized with aqueous $NaHCO_3$ and extracted with (60 mL × 3) of ethyl acetate. The organic layer was washed successively with water (30 mL × 2) and saturated brine (20 mL × 2), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give a crude product, which was purified using column chromatography (petroleum ether:ethyl acetate V/V 6:1) to afford **3e**–**f** and **3e′**–**f′**.

4.5.1. (3a*S*,4*R*,6a*R*)-*tert*-Butyl 2,2-dimethyl-4-((*R*)-4-oxo-3-phenylthiazolidin-2-yl)dihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate 3e

Pale yellow syrup, yield 47%; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H: 1.35–1.45 (15H, m, 5CH_3), 2.52–2.63 (1H, m, CH_2), 3.49–3.71 (2H, m, CH_2), 3.88 (1H, d, J = 16.2 Hz, CH_2), 4.23 (1H, s, CH), 4.61–4.62 (1H, m, CH), 4.66–4.68 (1H, m, CH), 5.74, 5.92 (1H, CH), 7.31–7.44 (5H, m, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 25.1, 26.9, 28.3, 32.5, 53.9, 62.5, 66.3, 79.6, 80.2, 81.0, 112.0, 126.5, 126.9, 129.6, 136.9, 154.2, 170.5; HRMS (ESI): Calcd for $C_{21}H_{28}N_2O_5SNa$ ([M+Na]$^+$): 443.1616. Found: 443.1620.

4.5.2. (3a*S*,4*R*,6a*R*)-*tert*-Butyl 2,2-dimethyl-4-((*S*)-4-oxo-3-phenylthiazolidin-2-yl)dihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate 3e′

Pale yellow syrup, yield 23%; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H: 1.35–1.45 (15H, m, 5CH_3), 3.64–3.69 (1H, m, CH_2), 3.75, 3.91 (1H, d, J = 12 Hz, CH_2), 3.78–3.83 (2H, m, CH_2), 4.15, 4.29 (1H, CH), 4.75 (1H, d, J = 6 Hz, CH), 4.82–4.87 (1H, m, CH), 5.45, 5.76 (1H, CH), 7.36–7.48 (5H, m, H-Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 24.9, 27.0, 28.3, 33.1, 53.3, 62.5, 68.9, 79.2, 80.2, 80.7, 112.3, 125.3, 127.2, 129.3, 154.1, 170.9; HRMS (ESI): Calcd for $C_{21}H_{28}N_2O_5SNa$ ([M+Na]$^+$): 443.1616. Found: 443.1621.

4.5.3. (3a*S*,4*R*,6a*R*)-*tert*-Butyl 4-((*R*)-3-(4-chlorophenyl)-4-oxothiazolidin-2-yl)-2,2-dimethyl-dihydro-3a*H*-[1,3]dioxolo [4,5-*c*]pyrrole-5(4*H*)-carboxylate 3f

Pale yellow syrup, yield 41%; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H: 1.32–1.37 (9H, m, 3CH_3), 1.43 (6H, s, 2CH_3), 3.61–3.65 (1H, m, CH_2), 3.75–3.80 (2H, m, CH_2), 3.73–3.74, 3.90–3.92 (1H, m, CH_2), 4.08, 4.23 (1H, CH), 4.69 (1H, d, J = 6.0 Hz, CH), 4.76–4.86 (1H, m, CH), 5.42, 5.71 (1H, CH), 7.30–7.44 (4H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 25.1, 27.0, 28.3, 66.2, 32.4, 53.8, 60.4, 63.3, 79.7, 80.1, 80.8, 112.2, 128.1, 129.8, 135.4, 154.2, 170.6; HRMS (ESI): Calcd for $C_{21}H_{27}ClN_2O_5SNa$ ([M+Na])$^+$: 477.1227. Found: 477.1225.

4.5.4. (3a*S*,4*R*,6a*R*)-*tert*-Butyl 4-((*S*)-3-(4-chlorophenyl)-4-oxothiazolidin-2-yl)-2,2-dimethyl-dihydro-3a*H*-[1,3]dioxolo [4,5-*c*]pyrrole-5(4*H*)-carboxylate 3f′

Pale yellow syrup; yield 21%. ^{1}H NMR (600 MHz, $CDCl_3$) δ_H: 1.44–1.52 (15H, m, 5CH_3), 3.03 (1H, dd, J = 12.6 Hz, 4.8 Hz, CH_2), 3.63–3.67 (1H, m, CH_2), 3.83 (1H, d, J = 14.4 Hz, CH_2), 3.63–3.67, 3.83 (1H, m, CH_2), 4.29–4.34 (1H, m, CH), 4.59 (1H, d, J = 5.4 Hz, CH), 4.69 (1H, t, J = 5.4 Hz, CH), 5.74 (1H, s, CH), 7.39 (4H, s, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 25.0, 27.0, 27.7, 28.3, 33.1, 54.0, 60.4, 63.4, 68.4, 79.4, 80.6, 81.2, 112.4, 126.6, 129.2, 154.4, 170.7; HRMS (ESI): Calcd for $C_{21}H_{27}ClN_2O_5SNa$ ([M+Na]$^+$): 477.1227. Found: 477.1228.

4.6. General procedure for the synthesis of 4a, 4c–4f and 4a′, 4e′–4f′

Compound **3a** (1.0 g, 1.8 mmol) was dissolved in 5 mL of 90% trifluoroacetic acid aqueous solution. The mixture was then stirred at rt for 1 h. After the reaction had finished, the solvent was removed under reduced pressure to give a crude product, which was purified using column chromatography (ethyl acetate:MeOH V/V 5:1) to give **4a**. According to the same procedure, compounds **4a′**, **4c**–**4f,** and **4e′**–**4f′** were obtained.

4.6.1. (*R*)-3-(((2*R*,3*S*,4*R*,5*R*)-3,4-Dihydroxy-5-methoxytetra hydrofuran-2-yl)methyl)-2-methyl)-2-((2*R*,3*S*,4*R*)-3,4-di hydroxypyrrolidin-2-yl)thiazolidin-4-one 4a

Yellow solid, yield 65%, mp 262.0 °C, $[\alpha]_D^{25} = +14.2$ (*c* 1.0, MeOH); ^{1}H NMR (600 MHz, CD_3OD) δ_H: 2.92 (1H, d, J = 12.0 Hz, 3.0 Hz, CH_2), 3.10 (1H, dd, J = 12.0 Hz, 4.8 Hz, CH_2), 3.38 (3H, s, –OCH_3), 3.53 (1H, dd, J = 15.0 Hz, 3.0 Hz, CH), 3.56 (1H, d, J = 15.6 Hz, CH), 3.68 (1H, d, J = 16.2 Hz), 3.79 (1H, q, J = 3.0 Hz, CH), 3.90 (1H, d, J = 4.2 Hz, CH), 4.01 (1H, dd, J = 14.4 Hz, 6.6 Hz, CH), 4.05–4.08 (2H, m, CH_2), 4.14–4.19 (2H, m, CH_2), 4.75 (1H, s, CH), 5.26 (1H, s, CH); ^{13}C NMR (125 MHz, CD_3OD) δ_C: 31.3, 46.2, 51.4, 54.5, 62.2, 64.6, 72.4, 72.7, 72.9, 74.8, 78.9, 108.8, 172.8; HRMS (ESI): Calcd for $C_{13}H_{23}N_2O_7S$ ([M+H]$^+$), 351.1226. Found: 351.1231.

4.6.2. (*S*)-3-(((2*R*,3*S*,4*R*,5*R*)-3,4-Dihydroxy-5-methoxytetra hydrofuran-2-yl)methyl)-2-methyl)-2-methyl)-2-((2*R*,3*S*,4*R*)-3,4-dihydroxypyrrolidin-2-yl)thiazolidin-4-one 4a′

White solid, yield 62%, mp 260.0 °C, $[\alpha]_D^{25} = -26.0$ (*c* 1.0, MeOH); ^{1}H NMR (600 MHz, CD_3OD) δ_H: 2.92 (1H, dd, J = 12.0 Hz, 2.4 Hz, CH_2), 3.13 (1H, dd, J = 12.6 Hz, 4.8 Hz, CH_2), 3.30 (3H, s, –OCH_3), 3.49 (1H, d, J = 15.0 Hz, CH), 3.71 (1H, dd, J = 13.8 Hz, 2.4 Hz, CH), 3.76 (1H, dd, J = 15.6 Hz, 1.8 Hz, CH), 3.84 (1H, dd, J = 9.6 Hz, 4.8 Hz, CH), 3.89 (1H, d, J = 4.8 Hz, CH), 4.03 (1H, dd, J = 7.2 Hz, 4.2 Hz, CH), 4.06–4.09 (2H, m, 2CH_2), 4.11–4.14 (2H, m, 2CH_2), 4.77 (1H, s, CH), 5.38 (1H, s, CH); ^{13}C NMR (125 MHz, CD_3OD) δ_C: 31.6, 46.2, 51.8, 54.7, 60.1, 64.6, 71.8, 73.3, 74.5, 74.6, 80.9, 108.9, 172.7; HRMS (ESI): Calcd for $C_{13}H_{23}N_2O_7S$ ([M+H]$^+$), 351.1226. Found: 351.1228.

4.6.3. (*R*)-2-((2*R*,3*S*,4*R*)-3,4-Dihydroxypyrrolidin-2-yl)-3-(((2*S*,3*S*,4*R*)-3,4-dihydroxypyrrolidin-2-yl)methyl)thiazolidin-4-one 4c

White solid, yield 80%, mp 110.1–111.3 °C, $[\alpha]_D^{25} = +31.1$ (*c* 1.0, H_2O); ^{1}H NMR (600 MHz, D_2O) δ_H: 2.87, 3.04, 3.13 (4H, 2CH_2), 3.41 (1H, dd, J = 13.2 Hz, 4.2 Hz, CH), 3.51 (1H, d, J = 16.2 Hz, CH), 3.58–3.65(2H, m, CH_2), 3.69 (1H, m, CH), 3.79 (1H, dd, J = 15.6 Hz, 3.6 Hz, CH), 3.95 (1H, dd, J = 9.6 Hz, 4.2 Hz, CH), 4.07 (1H, d, J = 3.0 Hz, CH), 4.16–4.19 (2H, m, CH), 5.04 (1H, s, CH); ^{13}C NMR (125 MHz, D_2O)

δ_C: 23.2, 31.4, 44.4, 50.4, 58.9, 61.6, 64.8, 68.8, 71.6, 72.5, 73.1, 175.5; HRMS (ESI): Calcd for $C_{12}H_{22}N_3O_5S$ ([M+H]$^+$), 320.1274. Found: 320.1274.

4.6.4. (*S*)-2-((2*R*,3*S*,4*R*)-3,4-Dihydroxypyrrolidin-2-yl)-3-(((2*S*,3*R*,4*R*,5*R*)-3,4,5-trihydroxypiperidin-2-yl)methyl)thiazolidin-4-one 4d

Pale yellow solid, yield 80%, mp 172.5–173.5 °C, $[\alpha]_D^{25} = +55.4$ (*c* 1.0, H_2O); ^{1}H NMR (600 MHz, D_2O) δ_H: 2.67 (1H, dd, *J* = 12.6 Hz, 10.8 Hz, CH), 2.84–2.92 (2H, m, CH_2), 3.04 (1H, dd, *J* = 12.6 Hz, 4.2 Hz, CH), 3.28–3.31 (2H, m, CH_2), 3.57 (1H, d, *J* = 16.8 Hz, CH), 3.63–3.65 (2H, m, 2CH), 3.67 (1H, dd, *J* = 16.2 Hz, 1.8 Hz, CH), 3.73 (1H, dd, *J* = 4.2 Hz, 0.6 Hz, CH), 3.89–3.93 (2H, m, CH_2), 4.09 (1H, m, CH), 4.15 (1H, dd, *J* = 7.2 Hz, 4.8 Hz, CH), 5.02 (1H, t, *J* = 4.8 Hz, CH); ^{13}C NMR (125 MHz, D_2O) δ_C: 31.8, 44.0, 44.2, 50.5, 50.9, 61.6, 64.8, 65.5, 68.9, 69.8, 72.7, 72.8, 174.7; HRMS (ESI): Calcd for $C_{13}H_{24}N_3O_6S$ ([M+H]$^+$), 350.1385. Found: 350.1381.

4.6.5. (*R*)-2-((2*R*,3*S*,4*R*)-3,4-Dihydroxypyrrolidin-2-yl)-3-phenylthiazolidin-4-one 4e

Pale yellow solid, yield 87%, mp 160.0 °C, $[\alpha]_D^{25} = +115.1$ (*c* 1.0, MeOH); ^{1}H NMR (600 MHz, CD_3OD) δ_H: 2.68 (1H, dd, *J* = 12.0 Hz, 3.0 Hz, CH_2), 2.95 (1H, dd, *J* = 11.4 Hz, 3.6 Hz, CH_2), 3.29 (1H, d, *J* = 3.6 Hz, CH), 3.55 (1H, d, *J* = 16.2 Hz, CH_2), 3.78 (1H, d, *J* = 15.6 Hz, CH_2), 3.94 (1H, d, *J* = 4.2 Hz, CH), 4.12 (1H, t, *J* = 5.4 Hz, CH), 5.32 (1H, s, CH), 7.22–7.38 (5H, m, ArH); ^{13}C NMR (125 MHz, CD_3OD) δ_C: 32.1, 50.9, 63.5, 66.9, 72.5, 72.8, 126.9, 127.5, 128.9, 137.7, 172.0; HRMS (ESI): Calcd for $C_{13}H_{17}N_2O_3S$ ([M+H]$^+$): 281.0960. Found: 281.0967.

4.6.6. (*S*)-2-((2*R*,3*S*,4*R*)-3,4-dihydroxypyrrolidin-2-yl)-3-phenylthiazolidin-4-one 4e′

White solid, yield 85%, mp 160.0 °C, $[\alpha]_D^{25} = -130.1$ (*c* 1.0, MeOH); ^{1}H NMR (600 MHz, CD_3OD) δ_H: 2.90 (1H, dd, *J* = 12.6 Hz, 1.8 Hz, CH_2), 3.15 (1H, dd, *J* = 12.0 Hz, 4.2 Hz, CH_2), 3.28 (1H, dd, *J* = 7.8 Hz, 1.2 Hz, CH), 3.63 (1H, d, *J* = 15.6 Hz, CH_2), 3.81 (1H, dd, *J* = 7.8 Hz, 4.2 Hz, CH), 3.97 (1H, dd, *J* = 15.6 Hz, 1.8 Hz, CH_2), 4.04 (1H, d, *J* = 1.8 Hz, CH), 5.49 (1H, s, CH), 7.25–7.39 (5H, m, ArH); ^{13}C NMR (125 MHz, CD_3OD) δ_C: 32.7, 52.2, 62.6, 67.2, 72.0, 74.9, 126.6, 127.6, 129.2, 137.2, 172.2; HRMS (ESI): HRMS (ESI): Calcd for $C_{13}H_{17}N_2O_3S$ ([M+H]$^+$): 281.0960. Found: 281.0964.

4.6.7. (*R*)-3-(4-Chlorophenyl)-2-((2*R*,3*S*,4*R*)-3,4-dihydroxy pyrrolidin-2-yl)thiazolidin-4-one 4f

Pale yellow liquid, yield 90%, $[\alpha]_D^{25} = +64.1$ (*c* 1.0, MeOH); ^{1}H NMR (600 MHz, CD_3OD) δ_H: 2.84 (1H, dd, *J* = 12.0 Hz, 3.6 Hz, CH_2), 3.09 (1H, dd, *J* = 12.0 Hz, 4.2 Hz, CH_2), 3.42 (1H, dd, *J* = 6.6 Hz, 3.0 Hz, CH), 3.69 (1H, d, *J* = 15.6 Hz, CH_2), 3.90 (1H, dd, *J* = 16.2 Hz, 1.8 Hz, CH), 4.07 (1H, d, *J* = 3.6 Hz, CH_2), 4.26 (1H, t, *J* = 6.0 Hz, CH), 5.48 (1H, s, CH), 7.46–7.52 (4H, m, ArH); ^{13}C NMR (125 MHz, CD_3OD) δ_C: 32.0, 51.1, 63.0, 66.6, 72.4, 72.9, 126.9, 127.8, 132.9, 136.4, 161.8, 171.9; HRMS (ESI): Calcd for $C_{13}H_{16}ClN_2O_3S$ ([M+H]$^+$): 315.0570. Found: 315.0572.

4.6.8. (*S*)-3-(4-Chlorophenyl)-2-((2*R*,3*S*,4*R*)-3,4-dihydroxy pyrrolidin-2-yl)thiazolidin-4-one 4f′

White solid, yield 88%, mp 155.0 °C, $[\alpha]_D^{25} = -67.0$ (*c* 1.0, MeOH); ^{1}H NMR (600 MHz, CD_3OD) δ_H: 2.90 (1H, d, *J* = 12.0 Hz, CH_2), 3.15 (1H, dd, *J* = 12.6 Hz, 4.8 Hz, CH_2), 3.27 (1H, d, *J* = 7.8 Hz, CH), 3.64 (1H, d, *J* = 15.0 Hz, CH_2), 3.83 (1H, q, *J* = 4.8 Hz, CH), 3.96 (1H, d, *J* = 15.6 Hz, CH_2), 4.06 (1H, s, CH), 5.50 (1H, s, CH), 7.43–7.50 (4H, m, ArH); ^{13}C NMR (125 MHz, CD_3OD) δ_C: 32.6, 52.2, 62.9, 66.8, 72.0, 74.8, 128.0, 129.2, 133.1, 135.9, 161.8, 172.2; HRMS (ESI): Calcd for $C_{13}H_{16}ClN_2O_3S$ ([M+H]$^+$): 315.0570. Found: 315.0568.

4.7. Synthesis of compound 4b

To a solution of **3b** (0.3 g, 0.4 mmol) in anhydrous MeOH (5 mL) was added MeONa (2 equiv). The mixture was then stirred at room temperature for 1 h under a nitrogen atmosphere. After the reaction had finished and neutralized with cationic resin, the filtrate was concentrated, then dissolved in 10 mL of 90% trifluoroacetic acid aqueous solution, and stirred at room temperature for 1 h. The solvent was removed under reduced pressure to give a crude product, which was purified using column chromatography (ethyl acetate:MeOH V/V 2:1) to give **4b**.

4.7.1. (*R*)-2-((2*R*,3*S*,4*R*)-3,4-Dihydroxypyrrolidin-2-yl)-3-(((2*R*,3*S*,4*S*,5*R*,6*S*)-3,4,5-trihydroxy-6-methoxytetrahydro-2*H*-pyran-2-yl)methyl)thiazolidin-4-one 4b

White solid, yield 50%, mp 106.2–108.3 °C, $[\alpha]_D^{25} = +123.0$ (*c* 1.0, CH_3OH); ^{1}H NMR (600 MHz, CD_3OD) δ_H: 2.93, 3.12 (2H, CH_2), 3.16 (1H, t, *J* = 9.6 Hz, CH), 3.41 (4H, m, –OCH_3, CH), 3.53 (1H, dd, *J* = 15.0 Hz, 2.4 Hz, CH), 3.58 (1H, d, *J* = 9.6 Hz, CH), 3.63 (1H, t, *J* = 9.0 Hz, CH), 3.71 (1H, dd, *J* = 15.6 Hz, 1.8 Hz, CH), 3.79 (2H, m, CH), 4.07 (1H, dd, *J* = 5.4 Hz, 3.6 Hz, CH), 4.14 (2H, m, CH), 4.67 (1H, d, *J* = 3.6 Hz, CH), 5.23 (1H, t, *J* = 3.6 Hz, CH); ^{13}C NMR (125 MHz, CD_3OD) δ_C: 31.3, 43.8, 51.4, 54.5, 61.9, 64.5, 69.0, 71.7, 72.1, 72.3, 72.9, 73.2, 99.9, 173.3; HRMS (ESI): Calcd for $C_{14}H_{25}N_2O_8S$ ([M+H]$^+$), 381.1326. Found: 381.1323.

4.8. X-ray crystallographic measurement of a single crystal of 4e′

Single crystals of compound **4e′** were obtained by recrystallization from a solution of EtOAc–MeOH and applied on a Bruker SMART CCD diffractometer for analysis. The intensity data were collected on a Bruker SMART CCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) using the $\theta/2\omega$ scan technique from a single crystal of 0.36 × 0.11 × 0.11 mm, and a semi-empirical absorption correction was applied for all complexes. The structure was solved by direct methods and refined by full-matrix least-squares on F^2. The absolute structure parameter was 0.08 (7), respectively. All non-hydrogen atoms were refined anisotropically.

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15. CCDC-911864 contains the supplementary crystallographic data for **4e**′. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.