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Journal Name

ARTICLE

Diversity-oriented synthesis of fused thioglycosyl benzo[*e*][1,4]oxathiepin-5-ones and benzo[*f*][1,4]thiazepin-5(2*H*)-ones by a sequences of palladium-catalyzed glycosyl thiol arylation and deprotection-lactonization reactions

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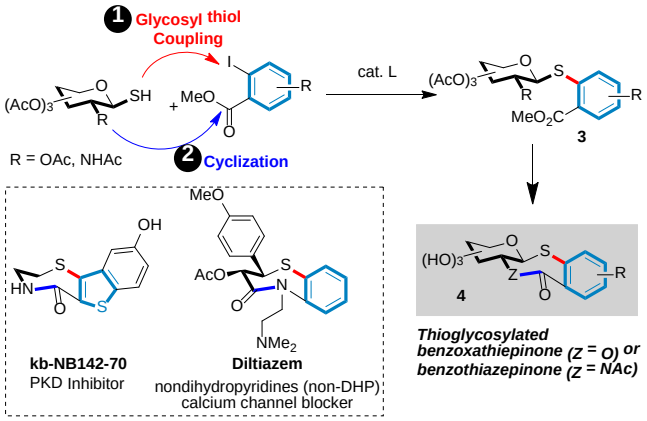
An efficient synthesis of thioglycosylated benzo[*e*][1,4]oxathiepin-5-one and benzothiazepinone derivatives by a sequence of a palladium-catalyzed glycosyl thiols arylation followed by deprotection-lactonization reactions has been reported. This diversity-oriented strategy enabled an access to unknown complex cyclic scaffolds with polyhydroxylated appendages of biological interests.

Introduction

Arylthioglycosides are an important family of natural or synthetic products that exhibit various biological activities[1] including control of hyperglycemia in diabete,[2] antibacterial[3] and anticancer[4] activities. Moreover, they are a rich source of building blocks to access complex architectures having various biological activities.[5] Thus, continuing demand to synthesize glycosides-based drugs requires the development of fast and easy synthetic methods. In this context, diversity-oriented synthesis[6] continues to be an essential area to generate libraries of molecules by varying functional groups, building blocks, stereochemistry, and molecular frameworks in order to obtain molecular diversity. However, carbohydrates remain relatively underexplored which is due in part to the difficulty associated with the chemistry related to sugars.

As part of our efforts on the development of efficient methods to functionalize carbohydrates *via* transition-metal catalysis for generating an original collection of heterosides,[7] we have disclosed that α- and β-glycosyl thiols can serve as effective nucleophiles for Buchwald-Hartwig type-coupling reactions using functionalized organic halides, including aryl, heteroaryl, alkenyl and alkynyl halides.[7a-c] The functional group tolerance on the electrophilic partner is typically high and anomer selectivities of thioglycosides are high in all cases studied. In our continuation to develop efficient methodologies to access complex heterosides, we envisioned that thioglycosides of type



Scheme 1. General strategy to fused thioglycosyl benzo[*e*][1,4]oxathiepin-5-ones and benzo[*f*][1,4]thiazepin-5(2*H*)-ones

3 could be utilized as partners in the synthesis of fused thioglycosyl benzoxathiepinones or benzothiazepinones through a cyclization reaction (Scheme 1). This modular strategy is conceptually attractive in terms of diversifying the benzoxathiepinone and benzothiazepinone frameworks with the aim to identify novel scaffolds of biological interest such as kb-NB142-70[8], a protein kinase D inhibitor, or Diltiazem[9], a marketed drug to treat hypertension, angina pectoris and some types of arrhythmia (Scheme 1). Herein, we described our findings on the sequential coupling/cyclization reactions of easily accessed substituted methyl 2-iodobenzoate and a wide range of glycosyl thiols to afford various fused thioglycosyl benzoxathiepinone and benzothiazepinone derivatives of type **4**.

Results and discussion

To achieve successfully our goal, we initially prepared

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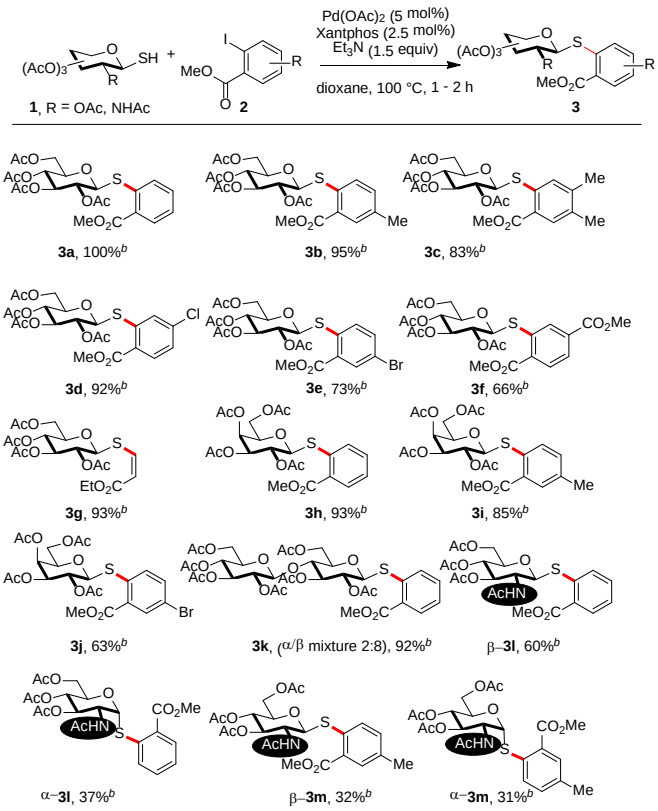
† Electronic Supplementary Information (ESI) available: 1H, 13C, COSY, HSQC, HMBC and NOESY NMR spectra. See DOI: 10.1039/x0xx00000x

Scheme 2: Pd-Catalyzed coupling of peracetylated glycosyl thiols **1** with various methyl 2-iodobenzoates **2**.[a]

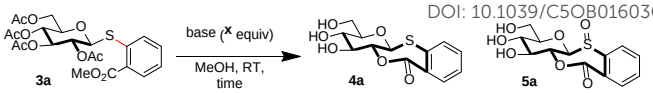


[a] Reactions of **1** (1 equiv) with **2** (1.2 equiv) were performed in a sealed tube at 100 °C in dioxane (0.05 M) by using $Pd(OAc)_2$ (5 mol%), Xantphos (2.5 mol%), NEt_3 (1.5 equiv). [b] Yield of isolated product.

selectively a series of thioglycosides of type **3** by coupling various substituted methyl 2-iodobenzoates with peracetylated glycosyl thiols under our previously reported protocol[7a] [$Pd(OAc)_2$ (5 mol%), Xantphos (2.5 mol%), NEt_3 (1.5 equiv), dioxane, 100 °C for 1 h] (Scheme 1).

As depicted in Scheme 2, peracetylated 1-thio-β-D-glucopyranose was readily coupled with methyl 2-iodobenzoate having *para* and *meta* electron-donating or electron withdrawing substituents to give thioglycosylated products **3a-f** in good to excellent yields with complete β-selectivity. Z-methyl-3-iodo-acrylate is also a suitable coupling partner with thioglycoside **1** furnishing stereoselectively β-thioglycosidated Z-alkene **3g** without any thermal isomerization, clearly demonstrating the mild nature of this cross-coupling reaction. In addition, the reaction is general with respect to the sugar configuration as peracetylated 1-thio-β-D-galactopyranose, *N*-acetyl-1-thio-β-D-aminoglucopyranose as well as peracetylated 1-thio-β-D-cellobiose give the corresponding products **3h-k** in good yields. Of note, that longer reaction time was required (12 h *vs* 1 to 2 h) for achieving complete conversion of the reaction of methyl 2-iodobenzoate derivatives with *N*-acetyl-1-thio-β-D-aminogluco-pyranose. In these cases, the coupling worked well (**3l**: 97%, **3m**: 63%), but furnished a mixture of α– and

Table 1. Optimization of the synthesis of **4a**[a]



Entry	Base (x equiv)	T(°C)	Time (h)	Ratio **4a**/**5a**[b]	Yield (%)[c]
1	K_2CO_3 (2)	50	12	0/100	62
2	K_2CO_3 (1)	20	2	0/100	87
3	MeONa (1)	20	2	0/100	82
4	MeONa (0.5)	20	2	56/44	-
5	K_2CO_3 (1)	20	0.16	100/0	99
6	K_2CO_3 (0.3)	20	0.5	100/0	99

[a] Conditions: To a mixture **3a** (0.1 mmol) and base in MeOH (3 mL) was stirred under argon atmosphere. [b] The ratio **4a**/**5a** was determined by ^{1}H NMR on the crude reaction mixture and is based on the chemical shift of the anomeric proton signal (ppm) (4.76 ppm for **4a** and 4.36 ppm for **5a**) [c] Yield of isolated compound.

β–anomers (β-**3l**/α-**3l 62:38;** β-**3m**/α-**3m 55:45**). After a separation by flash chromatography column, compounds β-**3l,** α-**3l**, β-**3m,** α-**3m** were easily isolated in 60%, 37%, 32% and 31%, respectively (Scheme 2).

Following the selective preparation of thioglycosides **3a-k**, we expected that after selective removing the *O*-acetyl groups, the resulting OH at C2' position of the sugar moiety can undergo further lactonization with the ester function of the aromatic nucleus to lead to disubstituted fused thioglycosyl benzoxathiepinones **4a-k**. To determinate the feasibility of the C-2 lactonization of intermediates **3a-k**, we examined at first, the Zemplen[10,11] deprotection/cyclization sequence of **3a** as a model study. To this end, various reaction conditions (base, solvent and temperature) were screened and representative results from this study are summarized in Table 1. It was found that the reaction of **3a** (1 equiv) in the presence of K_2CO_3 (2 equiv) for 12 h at 50 °C furnished exclusively the non-expected sulfoxide **5a** in a 62% yield (entry 1). Achieving the reaction at room temperature for 2 h with only 1 equivalent of K_2CO_3 also led to **5a** but with a better 87% yield (entry 2). A Similar yield of **5a** (82%) was obtained when sodium methoxide was used instead of K_2CO_3 (entry 3). Of note, sulfoxide **5a** arises from the oxidation of **4a** in the presence of base in methanol.[12] These results clearly indicate that the thioglycoside **4a** is highly sensitive to the oxidative process under our reaction conditions. Interestingly, reducing the amount of MeONa to 0.5 equivalent lead to a mixture of **4a**/**5a** in a 56:44 ratio (entry 4), while the desired non-oxidized thioglycoside **4a** was isolated exclusively when the reaction was performed in the presence of K_2CO_3 (1 equiv) at room temperature with a short time of 10 min (entry 5). In summary, the best conditions were found to require thioglycoside **3a** (1 equiv), K_2CO_3 (30 mol%) in MeOH (3 mL) as the solvent at room temperature for 30 min. Under these conditions, **4a** was isolated in a quantitative yield (entry 6).
Motivated by these results, we next explored the scope of the deprotection/lactonization sequence with previously synthesized thioglycosides **3a-k**. Gratifyingly, fused thioglycosyl

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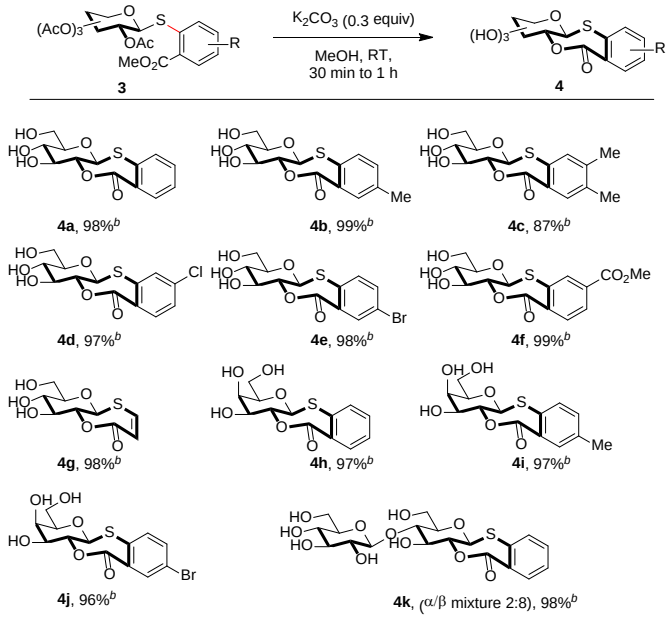
Scheme 3: Scope of the deprotection/cyclization reactions[a]



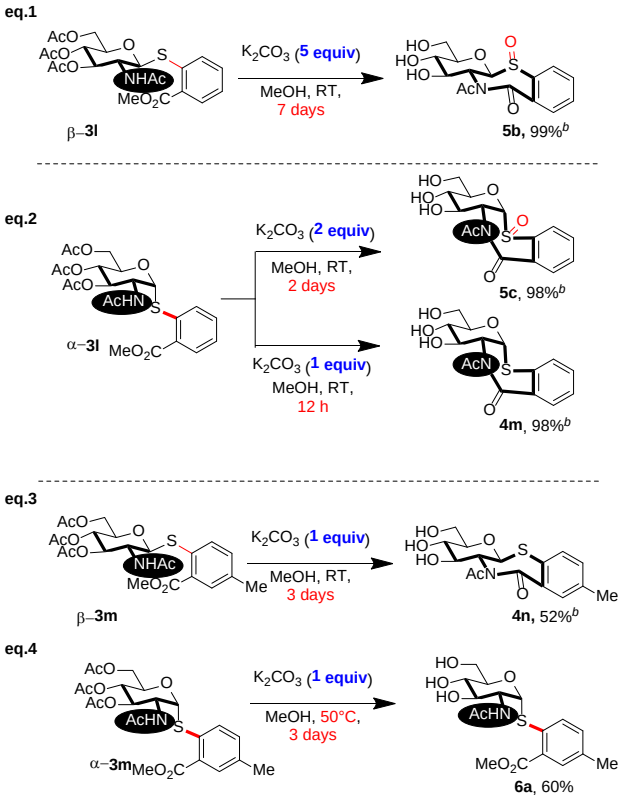
[a] Conditions: To a mixture **3** (0.1 mmol) and K_2CO_3 (0.3 equiv) in MeOH (1 mL) was stirred under argon atmosphere. [b] Yield of isolated compound.

benzoxathiepinones **4** bearing a wide variety of functional groups could be synthesized in good to excellent yields (Scheme 3). Electron-donating and electro-withdrawing functions on the aromatic ring, were well tolerated. The presence of C-Br and C-Cl bonds in compounds **4d,e** and **4j** provided a handle for further diversifications under transition metal-catalysis. It is noteworthy that the lactonization reaction of vinylthioglycose derivative **3g** having a *Z*-double bond, succeeded and leads to the formation of the bicyclic compound **4g** in a 98% yield.

In a further set of experiments, we investigated the scope and generality of the method with respect to substrates β-**3l**, **α-3l**, β-**3m** and **α-3m** bearing an *N*-acetyl function at C2' position of the sugar moiety (Scheme 4). It was found that the rate of the cyclisation step strongly depends on the nature of the nucleophile at the C2' position (*O- vs N*-nucleophile). Thus, when starting from **3a** the lactonization reaction took place within 10 min affording **4a** in an excellent yield, whereas the lactamization of the *N*-acetyl-1-thio-β-D-aminoglycoside β-**3l** was found to be sluggish. The cyclization step occurs only when five equivalents of the base were used during seven days stirring at room temperature. Under these conditions, removal of the *O*-acetate groups of the sugar moiety followed by the lactamization step as well as the sulfur atom oxidation lead to the benzothiazepinone oxide **5b** in a 99% yield (Scheme 4, eq. 1). Interestingly, when thioglycoside **α-3l** was used instead of it's anomer β–**3l**, only 2 equivalents of the base and 2 days reaction time were required for total conversion, leading to benzothiazepinone oxide **5c** in a quantitative yield without any anomerisation. This result clearly indicates that the lactamization reaction of the anomer α–**3l** is faster than β–**3l** probably for conformational considerations. In contrast to thioglycoside β–**3l**, when achieving the cyclization step from the anomer α–**3l** in the presence of only 1 equivalent of K_2CO_3, the α–thioglycoside **4m** was isolated in a quantitative yield and no trace of benzothiazepinone oxide was observed (Scheme 4, eq. 2).

To understand the influence of the electronic effects on the aromatic nucleus in the outcome of the lactamization step, a same study was conducted with α–**3m** and β–**3m** anomers having an additional methyl group on the aromatic nucleus. Surprisingly, the presence of this methyl group interferes in the rate of the lactamization step. In the case of the anomer β–**3m**, the cyclized product **4n** was obtained in a 52% yield when β–**3m** was stirred in the presence of 1 equivalent of the base during 3 days at room temperature, whereas, its anomer α–**3m could** never be cyclized even when the reaction was performed at 50 °C for 3 days. Under these conditions, the compound **6a**, resulting only from removal of the *O*-acetate groups of the sugar moiety, was isolated in a 60% yield.

Scheme 4: lactamization conditions of β-**3l, α-3l**, β-**3m, α-3m**[a]



[a] Conditions: To a mixture β-**3l, α-3l**, β-**3m, α-3m** (0.1 mmol) and K_2CO_3 in MeOH (1 mL) was stirred under argon atmosphere. [b] Yield of isolated compound.

To gain a better insight into the lactamization step of both β–**3l** and **α–3l** anomers (Scheme 4), we have carried out a computational study on the corresponding acetamide intermediates at the B3LYP/6-31G*[13] level. We have assumed that deacylation of the hydroxyl groups belonging to the pyrannose moiety happened early in this process, and that the rate-limiting step was the attack of the methyl ester group on the aromatic ring.

For each anomer, we have therefore tested two scenarios, starting from the free-hydroxy anionic intermediate, namely those in which the aromatic methyl ester is attacked on its *Si* or

Re face, and searched the potential energy surfaces for the cyclisation transition states. Comparison of the corresponding

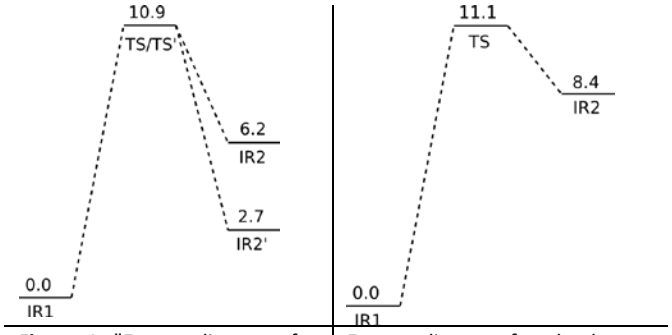


Figure 1. "Energy diagrams for the two possible cyclisation pathways of the α–3l. Free energies are indicated in kcal/mol. IR1 designates the open anionic intermediate, IR2 and IR2' the cyclised tetrahedral intermediates and TS/TS' the respective transition states." Energy diagram for the lowest energy cyclisation pathways of the β–3l. Free energies are indicated in kcal/mol. IR1 designates the open anionic intermediate, IR2 the cyclised tetrahedral intermediate and TS the transition state (not shown)

free energy profiles (10.9 Kcal and 11.1 kcal for **α–3l** and **β–3l**, respectively) (Figure 1) indicated that the pathways involving **α–3l** anomer were kinetically favoured. Moreover, as it is shown in Figure 2, no *Si* or *Re* face preference for the attack on the ester is found. The two alternative transition states (**A**) and (**B**) occur with a C–N distance of 2.00 and 1.98 A respectively (Figure 2), and with an attack angle of 109.8 or 108.6° for (**A**) and (**B**), respectively.

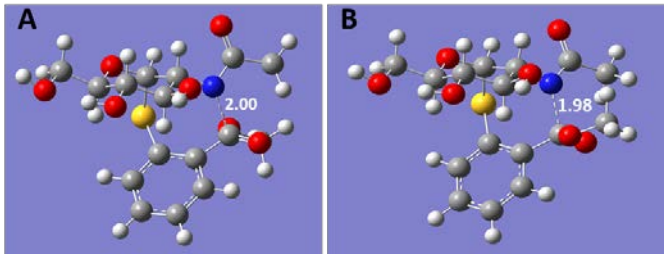


Figure 2. Geometries calculated at the B3LYP/6-31G* level for the two equiprobable transition states (**A:** *Re* face attack) and (**B:** *Si* face attack) leading to cyclisation of the **α-3l**.

Examination of the frontier molecular orbitals showed that the HOMO was mostly located around the nucleophilic nitrogen atom belonging to the acetamide, whereas the LUMO was distributed all over the aromatic carbonyl system (Figure 3). Moreover, a better overlap of the two FMO seemed possible in the case of the α-anomer than in the case of the β one, probably accounting for the difference of reactivity observed.

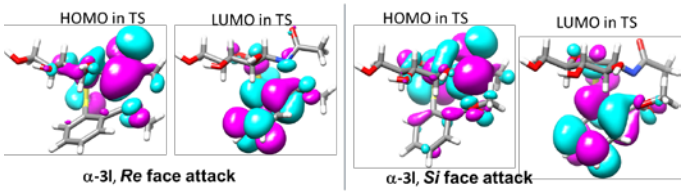


Figure 3. HOMO and LUMO for the *Re* and *Si* face attacks in the case of the anomer **α-3l**.

Conclusions

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In conclusion, we developed an efficient and practical protocol for the synthesis of substituted fused thioglycosyl benzoxathiepinones and benzothiazepinones. This transformation exhibited broad substrate scope with respect to both the aryl iodides and thiosugar partners. We believe that this methodology should find broad applications in synthetic organic chemistry, as well as in the combinatorial and pharmaceutical sciences.

Experimental

General experimental methods

The compounds were all identified by usual physical methods, e.g., 1H NMR, 13C NMR, IR, MS (ESI). 1H and 13C NMR spectra were measured in CDCl3, DMSO-d6 with a Bruker Avance-300. 1H chemical shifts are reported in ppm from an internal standard TMS or of residual solvent peak. 13C chemical shifts are reported in ppm from the residual solvent peak. IR spectra were measured on a Bruker Vector 22 spectrophotometer. Analytical TLC was performed on Merck precoated silica gel 60F plates. Merck silica gel 60 (0.015–0.040 mm) was used for column chromatography. Melting points were recorded on a Büchi B-450 apparatus and are uncorrected. High resolution mass spectra (HR-MS) were recorded on a Bruker MicroTOF spectrometer, using ESI with methanol as the carrier solvent. Nominal and exact m/z values are reported in Daltons.

General information

All reactions were conducted under argon atmosphere. Solvents: Cyclohexane, Ethyl acetate (EtOAc), Methanol (MeOH), Acetone, Dioxane and dichloromethane (CH_2Cl_2) for extraction and chromatography were technical grade

Experimental Section

Instrumentation

The compounds were all identified by usual physical methods, i.e.; ^{1}H NMR, ^{13}C NMR (J-MOD), IR, MS (ESI, APCI), 2D NMR. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$, $MeOD_4$ or $DMSO_4$.d_6, with a Bruker Avance-300. ^{1}H chemical shifts are reported in ppm from an internal standard TMS or of residual chloroform (7.27 ppm) or residual MeOH (3.3 ppm). The following observations are used: s (singlet), d (doublet), t (triplet), dd (douplet of doublet), m (multiplet), td (triplet of doublet), q (quadruplet). ^{13}C chemical shifts are reported in ppm from the central peak of deteriorated chloroform (77.14 ppm) or deteriorated methanol (49.0 ppm). IR spectra were measured on a Bruker Vector 22 spectrometer and are reported in wave numbers(cm^{-1}).Reaction courses and products were routinely monitored by analytical TLC which were performed on Merk precoated silica gel plates (60-F_{254}).Flash chromatography was performed on silica gel 60 (0.040-0.063 mm) and compounds were visualized under a UVP Mineralight UVGL-58 lamp (254 nm) and with

vanillin/Δ, or phosphomolybdic acid/Δ. Melting points (mp) were recorded on a Büchi B-450 apparatus and were uncorrected.

Typical procedure for Pd-catalyzed coupling of thioglycosides (1) with various substituted methyl 2-iodobenzoates (2).

A flame dried re-sealable Schlenk tube (5 ml) was charged with $Pd(OAc)_2$ (5 mmol%), Xantphos (2.5 mol%), thioglycosides (0.54 mmol, 1.5 equiv), methyl-2-iodobenzoates (0.36 mmol, 1.0 equiv). The Schlenk tube was capped with a rubber septum, evacuated and backfilled with argon; then, dioxane (1.5 ml) and Et_3N (0.36 mmol, 1.5 equiv) were added through the septum. The septum was replaced with a Teflon screw cap. The Schlenk tube was sealed and the mixture was stirred at 100 °C for 1 h. The resulting suspension was cooled to room temperature and filtered through celite eluting with ethyl acetate. The filtrate was concentrated and the residue purified by flash chromatography over silica gel to afford the desired intermediate products **(3a-m)**.

(2R,3R,4S,5R,6S)-2-(acetoxymethyl)-6-((2-(methoxycarbonyl)phenyl)thio)tetrahydro-2H-pyran-3,4,5-triyl triacetate (3a).

Following the general procedure of coupling, a mixture of thioglucose **1a** (200 mg, 0.54 mmol) and methyl 2-iodobenzoate **2a** (94.5 mg, 0.36 mmol) was heated for 1 h. The residue was purified by flash chromatography over silica gel (cyclohexane: ethyl acetate 7:3) to afford the desired product **3a** (179 mg, 0.36 mmol, 100%) as a white solid; **mp** (136.5-137.5°C); TLC: $\mathbf{R_f}$ = 0.5 (Cyclohexane: ethyl acetate 1:1); **IR** (thin film, neat) ν_{max}/cm^{-1}: 1755, 1714, 1644, 1467, 1435, 1367, 1253, 1212, 1112, 1037, 913, 829, 748; **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm): 7.82 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.52 (d, *J* = 7.2 Hz, 1H), 7.39 (td, *J* = 7.7, 1.6 Hz, 1H), 7.23 (td, *J* = 7.7, 1.1 Hz, 1H), 5.22 (dd, *J* = 12.0, 6.4 Hz, 1H), 5.04 (td, *J* = 9.8, 2.1 Hz, 2H), 4.82 (d, *J* = 10.1 Hz, 1H), 4.13 (qd, *J* = 12.3, 4.1 Hz, 2H), 3.83 (s, 3H), 3.79 – 3.69 (m, 1H), 2.01 (s, 3H), 1.97 (s, 3H), 1.97 (s, 3H), 1.94 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm): 170.7 (C=O), 170.3 (C=O), 169.5 (C=O), 169.3 (C=O), 166.9 (C=O), 136.7 (C), 132.4 (CH), 131.0 (C) 130.9 (CH), 129.6 (CH), 126.5 (CH), 84.5 (CH), 77.2 (CH), 75.9 (CH), 74.1(CH), 69.9(CH), 68.5, 62.5 (CH_2), 52.4 (CH_3), 20.9 (CH_3), 20.8 (CH_3), 20.7 ($2CH_3$); **HR-MS(ESI)**: for $C_{22}H_{26}O_{11}S$ (M + Na)$^+$: *m/z* calcd 521.1094, found 521.1099.

(2R,3R,4S,5R,6S)-2-(acetoxymethyl)-6-((2-(methoxycarbonyl)-4-methylphenyl)thio)tetrahydro-2H-pyran-3,4,5-triyl triacetate (3b).

Following the general procedure of coupling, a mixture of thioglucose **1a** (200 mg, 0.54 mmol) and methyl 2-iodo-5-methylbenzoate **2b** (99.5 mg, 0.36 mmol) was heated for 1 h. The residue was purified by flash chromatography over silica gel (Cyclohexane: ethyl acetate 7:3 to 4:6) to afford the desired product **3b** (175.0 mg, 0.341 mmol, 95%) as a beige solid; **mp** (136.5-137.5 °C); TLC: $\mathbf{R_f}$ = 0.5 (Cyclohexane: ethyl acetate 1:1); **IR** (thin film, neat) ν_{max}/cm^{-1}: 1755, 1715, 1475, 1435, 1367, 1300, 1248, 1210, 1115, 1090, 1036, 978, 914, 827, 785 ; **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm):7.66 (s, 1H), 7.50 (d, J = 8.1 Hz, 1H), 7.27 (d, J = 21.8 Hz, 1H), 5.25 (t, *J* = 9.3 Hz, 1H), 5.07 (td, *J* = 9.5, 7.8 Hz, 2H), 4.82 (d, *J* = 10.1 Hz, 1H), 4.19 (qd, *J* = 12.3, 3.9 Hz, 2H), 3.87 (s, 3H), 3.78 (dd, J = 10.0, 5.4, 2.4 Hz, 1H), 2.35 (s, 3H), 2.08 (s, 3H), 2.02 (s, 6H), 1.99 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm):170.9 (C=O), 170.6 (C=O), 169.8 (C=O), 169.60(C=O), 167.5 (C=O), 137.4 (C), 133.4 (CH), 132.4 (C), 132.1 (C), 131.6 (CH), 131.1 (CH), 85.2 (CH), 76.1 (CH), 74.4 (CH), 70.2 (CH), 68.7 (CH), 62.7 (CH_2), 52.6 (CH_3), 21.2 (CH_3), 21.2 (CH_3), 21.1 (CH_3), 21.0 ($2CH_3$); **HR-MS(ESI)**: for $C_{23}H_{28}O_{11}$(M + Na)$^+$: *m/z* calcd 535.1250, found 535,1251.

(2R,3R,4S,5R,6S)-2-(acetoxymethyl)-6-((2-(methoxycarbonyl)-4,5-dimethylphenyl)thio)tetrahydro-2H-pyran-3,4,5-triyl triacetate (3c).

Following the general procedure of coupling, a mixture of thioglucose **1a** (200 mg, 0.54 mmol) and methyl 2-iodo-4,5-dimethylbenzoate **2c** (104.5 mg, 0.36 mmol) was heated for 1 h., The residue was purified by flash chromatography over silica gel (Cyclohexane: ethyl acetate 8:2) to afford the desired product **3c** (158 mg, 0.244 mmol, 83%) as a white solid; **mp** (114.5-115.5°C); TLC: $\mathbf{R_f}$ = 0.63 (Cyclohexane: ethyl acetate1:1); **IR** (thin film, neat) ν_{max}/cm^{-1}: 1755 ,1746 ,1712 ,1603 ,1549, 1486, 1434, 1366, 1306, 1285, 1225, 1209, 1161, 1124, 1089, 1062, 1034, 978, 937, 914, 828, 808, 784, 736, 702, 675, 645; **^{1}H NMR**(300 MHz, CDCl3) δ(ppm):7.64 (s, 1H), 7.36 (s, 1H), 5.31 – 5.22 (m, 1H), 5.07 (dd, *J* = 19.3, 8.0 Hz, 2H), 4.84 (d, *J* = 10.1 Hz, 1H), 4.21 (dt, *J* = 25.8, 7.7 Hz, 2H), 3.86 (s, 3H), 3.80 (dd, *J* = 7.7, 5.4 Hz, 1H), 2.30 (s, 3H), 2.25 (d, *J* = 5.6 Hz, 3H), 2.07 (s, 3H), 2.03 (s, 6H), 1.99 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm): 170.7 (C=O), 170.3 (C=O), 169.5 (C=O), 169.3 (C=O), 167.1 (C=O), 141.6 (C), 135.6 (C), 132.6 (C), 131.9 (CH), 131.8 (CH), 129.0 (C), 84.9 (CH), 75.8 (CH), 74.5 (CH), 69.9 (CH), 68.4 (CH), 62.6 (CH_2), 52.1 (CH_3), 20.8 (CH_3), 20.8 (CH_3), 20.7 ($2CH_3$), 20.3 (CH_3), 19.3 (CH_3); **HR-MS(ESI)**: for $C_{24}H_{30}O_{11}S$ (M + Na)$^+$: *m/z* calcd 549.1407 found 549.1409.

(2R, 3R, 4S, 5R, 6S) – 2 - (acetoxymethyl) - 6 - ((5 – chloro – 2 - (methoxycarbonyl) phenyl) thio) tetrahydro - 2H – pyran – 3 , 4 ,5 -triyl triacetate (3d).

Following the general procedure of coupling, a mixture of thioglucose **1a** (200 mg, 0.54 mmol) and methyl 4-chloro-2-iodobenzoate **2d** (106.5 mg, 0.36 mmol) was heated for 1 h., The residue was purified by flash chromatography over silica gel (Cyclohexane: ethyl acetate 7:3 to 4:6) to afford the desired product **3d** (147 mg, 0.244 mmol, 92%) as a white to light yellow solid; **mp** (182-183°C), TLC: $\mathbf{R_f}$ = 0.64 (Cyclohexane: ethyl acetate 1:1); **IR** (thin film, neat) vmax/cm^{-1}:1745, 1722, 1581, 1552, 1466, 1433, 1383, 1366, 1300, 1244, 1215, 1111, 1085, 1032, 975, 921, 834, 768, 736, 684; **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm): 7.91 (d, *J* = 8.4 Hz, 1H), 7.58 (d, *J* = 2.0 Hz, 1H), 7.28 (dd, J = 8.5, 2.0 Hz, 1H), 5.34 (dd, *J* = 11.1, 7.4 Hz, 1H), 5.14 (dt, *J* = 11.8, 9.8 Hz, 2H), 4.94 (d, *J* = 10.1 Hz, 1H), 4.23 (d, *J* = 4.3 Hz, 2H), 3.95 (d, *J* = 4.0 Hz, 1H), 3.92 (s, 3H), 2.14 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm): 170.8 (C=O), 170.2 (C=O), 169.5 (C=O), 169.2 (C=O), 139.9 (C), 138.8 (C), 132.3 (CH), 128.2 (CH), 128.0 (C), 126.2 (CH), 83.9 (CH),

76.1 (CH), 74.1 (CH), 69.8 (CH), 68.4 (CH), 62.6 (CH_2), 52.5 (CH_3), 20.9 (CH_3), 20.8 (CH_3), 20.7 ($2CH_3$); **HR-MS(ESI)**: for $C_{22}H_{25}ClO_{11}S$ $(M + Na)^+$: *m/z* calcd 555.00704, found 555.0702.

(2R,3R,4S,5R,6S)-2-(acetoxymethyl)-6-((4-bromo-2-(methoxycarbonyl)phenyl)thio)tetrahydro-2H-pyran-3,4,5-triyl triacetate (3e).

Following the general procedure of coupling, a mixture of thioglucose **1a** (200 mg,0.54mmol) and methyl 5-bromo-2-iodobenzoate **2e** (123 mg, 0.36 mmol) was heated for 1 h. The residue was purified by flash chromatography over silica gel (Cyclohexane: ethyl acetate 7:3 to 4:6) to afford the desired product **3e** (152.0 mg, 0.26 mmol, 73%)as a beige rosee solid; **mp** (114.5-115.5 °C); TLC: $\mathbf{R_f}$ = 0.64 (Cyclohexane: ethyl acetate 1:1); **IR** (thin film, neat) ν_{max}/cm^{-1}: 1755, 1719, 1461, 1435, 1366, 1299, 1240, 1208, 1114, 1088, 1030, 961, 913, 826, 782, 734, 702; **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm): 8.00 (d, *J* = 2.2 Hz, 1H), 7.55 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.47 (d, *J* = 8.6 Hz, 1H), 5.31 – 5.21 (m, 1H), 5.13 – 5.03 (m, 2H), 4.83 (d, *J* = 10.1 Hz, 1H), 4.18 (qd, *J* = 12.3, 4.0 Hz, 2H), 3.88 (s, 3H), 3.78 (dd, *J* = 8.8, 4.3 Hz, 1H), 2.07 (s, 3H), 2.02 (s, 3H), 1.99 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm): 171.0 (C=O), 170.7 (C=O), 169.9 (C=O), 169.7 (C=O), 166.0 (C=O), 135.9 (C), 135.5 (CH), 134.1 (C), 133.1 (C), 131.9 (CH), 120.9 (CH), 84.7 (CH), 76.4 (CH), 74.4 (CH), 70.3 (CH), 68.8 (CH), 62.8 (CH_2), 53.1 (CH), 27.4 (CH_3), 21.3 (CH_3), 21.2 (CH_3), 21.1 ($2CH_3$); **HR-MS(ESI)**: for $C_{22}H_{25}BrO_{11}S$ $(M + Na)^+$: *m/z* calcd 599.0199, found 599.0206.

Dimethyl 2-(((2S,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)thio)terephthalate (3f).

Following the general procedure of coupling, a mixture of thioglucose **1a** (200 mg, 0.54 mmol) and dimethyl 2-iodoterephthalate **2f** (104.5 mg, 0.36 mmol) was heated for 1 h., The residue was purified by flash chromatography over silica gel (Cyclohexane: ethyl acetate 7:3) to afford the desired product **3f** (85 mg, 0.15 mmol, 66%) as a light beige solid **mp** (155.5-156.5°C); TLC: $\mathbf{R_f}$ = 0.63 (Cyclohexane: ethyl acetate1:1); **IR** (thin film, neat) ν_{max}/cm^{-1}: 1746, 1722, 1433, 1383, 1365, 1288, 1246, 1215, 1153, 1126, 1115, 1084, 1035, 979, 920, 897, 857, 828, 745; **^{1}H NMR** (300 MHz, CDCl3) δ (ppm): 8.24 (d, *J* = 1.2 Hz, 1H), 7.92 (dt, *J* = 8.1, 4.7 Hz, 2H), 5.31 (dd, *J* = 11.1, 7.3 Hz, 1H), 5.16 (t, *J* = 9.6 Hz, 2H), 4.97 (d, *J* = 10.0 Hz, 1H), 4.29 (dd, *J* = 12.4, 5.2 Hz, 2H), 4.18 (dd, *J* = 12.4, 2.1 Hz, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 2.04 (d, *J* = 2.3 Hz, 9H), 2.01 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm): 170.8 (C=O), 170.2 (C=O), 169.5 (C=O), 169.3 (C=O), 166.2 (C=O), 165.7 (C=O), 137.7 (C), 133.7 (C), 133.5 (C), 130.9 (CH), 129.9(CH), 126.9 (CH), 84.1 (CH), 76.0(CH), 74.1 (CH), 69.8 (CH), 68.2 (CH), 62.1 (CH_2), 52.7 (CH_3), 52.6 (CH_3), 30.0 (CH_3), 20.7 (CH_3), 20.7 ($2CH_3$); **HR-MS(ESI)**: for $C_{24}H_{30}O_{11}S$ $(M + Na)^+$: *m/z* calcd 579.1148 found 579.1144.

(2R,3R,4S,5R,6S)-2-(acetoxymethyl)-6-(((Z)-3-ethoxy-3-oxoprop-1-en-1-yl)thio)tetrahydro-2H-pyran-3,4,5-triyl triacetate (3g).

Following the general procedure of coupling, a mixture of thioglucose **1a** (200 mg,0.54mmol) and (Z)-ethyl 3-iodoacrylate **2g** (81.5 mg,0.36 mmol) was heated for 1 h., The residue was purified by flash chromatography over silica gel (Cyclohexane: ethyl acetate 7:3) to afford the desired product **3g** (76 mg, 0.33 mmol, 93%) as a white solid; **mp** (163-164°C); TLC: $\mathbf{R_f}$ = 0.5 (Cyclohexane:ethyl acetate 1:1); **IR** (thin film, neat) ν_{max}/cm^{-1}: 3481, 3359, 3215, 3182, 3090, 2188, 2161, 1756,1699, 1580, 1374, 1215, 1171, 1093, 1061, 1034, 915, 804; **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm): 7.29 – 7.16 (m, 1H), 5.99 (d, *J* = 10.1 Hz, 1H), 5.29 – 5.10 (m, 3H), 4.62 (d, *J* = 9.9 Hz, 1H), 4.31 – 4.10 (m, 4H), 3.85 – 3.74 (m, 1H), 2.08 (s, 3H), 2.03 (s, 6H), 2.01 (s, 3H), 1.28 (t, J = 7.5 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm): 170.66(C=O), 170.22(C=O), 169.40(C=O), 169.14(C=O), 166.42(C=O), 142.21(CH), 115.73(CH), 83.05(CH), 76.57(CH), 73.86(CH), 70.15(CH), 68.11(CH), 62.03(CH_2), 60.55(CH), 20.80(CH_3), 20.70(CH_3), 20.65($2CH_3$), 14.38(CH_3); **HR-MS (ESI)**: for $C_{19}H_{26}O_{11}S$ $(M + Na)^+$: *m/z* calcd 485.1094, found 485.1096.

(2R,3R,4S,5R,6S)-2-(acetoxymethyl)-6-((2-(methoxycarbonyl)phenyl)thio)tetrahydro-2H-pyran-3,4,5-triyl triacetate (3h).

Following the general procedure of coupling, a mixture of thiogalactose **1b** (200 mg, 0.54 mmol) and methyl 2-iodobenzoate **2a** (94.5 mg, 0.36 mmol) was heated for 1 h. The residue was purified by flash chromatography over silica gel (Cyclohexane:ethyl acetate 7:3-4:6) to afford the desired product **3h** (167 mg, 0.33 mmol, 93%)as a beige solid; **mp** (54.3-55.3 °C); TLC: $\mathbf{R_f}$ = 0.53 (Cyclohexane: ethyl acetate 1:1); **IR** (thin film, neat) ν_{max}/cm^{-1}: 2922, 1746, 1712, 1588, 1565, 1468, 1435, 1367, 1295, 1253, 1208, 1144, 1110, 1083,1058, 1039, 1015, 950, 917, 897, 828, 750, 734, 655; **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm): 8.15 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.72 (td, *J* = 7.8, 1.6 Hz, 1H), 7.56 (ddd, *J* = 7.6, 6.7, 1.1 Hz, 1H), 5.74 (dd, *J* = 3.2, 0.6 Hz, 1H), 5.68 – 5.56 (m, 1H), 5.38 (dd, J = 9.9, 3.4 Hz, 1H), 5.15 (d, *J* = 10.0 Hz, 1H), 4.43 (qd, *J* = 11.3, 6.5 Hz, 2H), 4.30 (t, *J* = 6.5 Hz, 1H), 4.17 (s, 3H), 2.44 (s, 3H), 2.32 (d, J = 2.0 Hz, 6H), 2.26 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm): 170.73(C=O), 170.61(C=O), 170.43(C=O), 169.69(C=O), 167.17(C=O), 137.25(C), 132.56(CH), 131.15(CH), 131.04(C), 129.73(CH), 126.63(CH), 85.12(CH), 74.83(CH), 72.45(CH), 67.70(CH), 67.30(CH), 62.23(CH_2), 52.58(CH_3), 21.13(CH_3), 21.06($2CH_3$), 20.97(CH_3); **HR-MS (ESI)**: for $C_{22}H_{26}O_{11}S$ $(M + Na)^+$: *m/z* calcd 521.1094, found 521.1091.

(2R,3S,4S,5R,6S)-2-(acetoxymethyl)-6-((2-(methoxycarbonyl)-4-methylphenyl)thio)tetrahydro-2H-pyran-3,4,5-triyl triacetate (3i).

Following the general procedure of coupling, a mixture of thiogalactose **1b** (200 mg, 0.54 mmol) and methyl 2-iodo-5-methylbenzoate **2b** (94.5 mg, 0.36 mmol) was heated for 1 h., The residue was purified by flash chromatography over silica gel (Cyclohexane: ethyl acetate 7:3-5:5) to afford the desired product **3i** (131 mg, 0.22 mmol, 85%) as an intense beige solid; **mp** (95-96 °C); TLC: $\mathbf{R_f}$ = 0.58 (Cyclohexane : ethyl acetate 1:1); **IR** (thin film, neat) ν_{max}/cm^{-1}: 1747, 1713, 1475, 1435, 1367, 1299, 1247, 1205, 1153, 1113, 1083, 1055, 1035, 950, 917, 897, 824, 785, 734, 702; **^{1}H NMR**

(300 MHz, $CDCl_3$) δ (ppm)7.63 (d, *J* = 1.5 Hz, 1H), 7.52 (d, *J* = 8.1 Hz, 1H), 7.22 (dd, *J* = 8.2, 1.6 Hz, 1H), 5.42 (d, *J* = 2.8 Hz, 1H), 5.28 (dd, *J* = 12.4, 7.6 Hz, 1H), 5.06 (dd, *J* = 9.9, 3.4 Hz, 1H), 4.79 (d, *J* = 10.0 Hz, 1H), 4.12 (qd, *J* = 11.3, 6.5 Hz, 2H), 3.96 (t, *J* = 6.5 Hz, 1H), 3.85 (s, 3H), 2.33 (s, 3H), 2.13 (s, 3H), 2.01 (d, J = 1.3 Hz, 6H), 1.95 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm): 170.8 (C=O), 170.7 (C=O), 170.5 (C=O), 169.8 (C=O), 167.5 (C=O), 137.2 (C), 133.3 (CH), 132.9 (C), 131.9 (C), 131.6 (CH), 130.9 (CH), 85.8 (CH), 74.8 (CH), 72.5 (CH), 67.7 (CH), 67.4 (CH), 62.2 (CH_2), 52.6 (CH_3), 21.2 ($2CH_3$), 21.1 ($2CH_3$), 21.0 (CH_3); **HR-MS (ESI)**: for $C_{23}H_{28}O_{11}S$ (M + Na)$^+$: *m/z* calcd 535.1250, found 535.1252.

(2R,3S,4S,5R,6S)-2-(acetoxymethyl)-6-((4-bromo-2-(methoxycarbonyl)phenyl)thio)tetrahydro-2H-pyran-3,4,5-triyl triacetate (3j).

Following the general procedure of coupling, a mixture of thiogalactose **1b** (200 mg, 0.54 mmol) and methyl methyl 5-bromo-2-iodobenzoate **2e** (123 mg, 0.36 mmol) was heated for 1 h. The residue was purified by flash chromatography over silica gel (Cyclohexane: ethyl acetate 7:3-5:5) to afford the desired product **3j** (131 mg, 0.22 mmol, 63%) as an intense beige solid; **mp** (95-96 °C); TLC: R_f = 0.58(Cyclohexane: ethyl acetate 1:1); **IR** (thin film, neat) ν_{max}/cm^{-1}: 1747, 1718, 1593, 1461, 1435, 1367, 1298, 1239, 1209, 1153, 1110, 1083, 1052, 1036, 966, 950, 917, 898, 821, 782, 734, 703; **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm): 8.07 – 7.94 (m, 1H), 7.55 (d, *J* = 1.3 Hz, 2H), 5.46 (dd, *J* = 3.3, 0.9 Hz, 1H), 5.32 (dd, *J* = 14.2, 5.7 Hz, 1H), 5.09 (dd, *J* = 9.9, 3.3 Hz, 1H), 4.82 (d, *J* = 10.0 Hz, 1H), 4.21 – 4.08 (m, 2H), 4.03 – 3.97 (m, 1H), 3.90 (s, 3H), 2.16 (s, 3H), 2.04 (d, J = 4.3 Hz, 6H), 1.98 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm): 170.43(C=O), 170.25(C=O), 170.15(C=O), 169.39(C=O), 165.66(C=O), 135.83(C), 135.04(CH), 133.68(CH), 132.57(C), 131.45(CH), 120.37(C), 84.77(CH), 74.72(CH), 72.11(CH), 67.34(CH), 66.93(CH), 61.88(CH_2), 52.61(CH_3), 29.82(CH_3), 20.82($2CH_3$), 20.70(CH_3); **HR-MS (ESI)**: for $C_{22}H_{25}BrO_{11}S$(M + Na)$^+$: *m/z* calcd 599.0199, found 599.0195.

(2R,3R,4S,5R,6S)-2-(acetoxymethyl)-6-(((2R,3R,4S,5R,6S)-4,5-diacetoxy-2-(acetoxymethyl)-6-((2-(methoxycarbonyl)phenyl)thio)tetrahydro-2H-pyran-3-yl)oxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (3k).

Following the general procedure of coupling, a mixture of thiocellobiose **1c** (352.5 mg, 0.54 mmol) and methyl 2-iodobenzoate **2a** (94.5 mg, 0.36 mmol) was heated for 12 hrs. The residue was purified by flash chromatography over silica gel (Cyclohexane: ethylacetate 7:3) to afford the desired product **3k** as a mixture of anomers α/β (2:8), (130 mg, 0.165 mmol, 92%) as a white solid; **mp** (192-193 °C); TLC: R_f = 0.43 (Cyclohexane: ethylacetate 1:1); **IR** (thin film, neat) ν_{max}/cm^{-1}: 1745, 1597, 1366, 1208, 1166, 1031, 905, 735, 703, 670, 654; **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm): 7.92 (dt, J = 6.2, 1.6 Hz, 2H), 7.62 (dd, *J* = 29.2, 7.4 Hz, 2H), 7.47 (td, *J* = 7.7, 1.6 Hz, 2H), 7.35 – 7.26 (m, 2H), 5.34 – 5.05 (m, 4H), 5.01 – 4.85 (m, 2H), 4.58 – 4.50 (m, 2H), 4.41 (dd, *J* = 12.5, 4.4 Hz, 1H), 4.23 – 4.04 (m, 2H), 3.94 (d, *J* = 13.2 Hz, 3H), 3.78 (dt, *J* = 24.7, 8.8 Hz, 3H), 2.12 (d, *J* = 5.8 Hz, 6H), 2.06 (dd, *J* = 5.1, 4.0 Hz, 12H), 2.01 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm): 170.6 (2C=O), 170.3 (2C=O), 169.9 (2C=O), 169.5 (2C=O), 169.4 (2C=O), 169.2 (2C=O), 169.1 (2C=O), 166.8 (2C=O), 137.2 (C), 136.7 (C), 132.5 (CH), 132.4 (CH), 130.9 (2CH), 130.6 (C), 130.4 (C), 129.5 (CH), 129.0 (CH), 126.3 (CH), 126.1 (CH), 100.9 (CH), 100.8 (CH), 84.1 (CH), 82.6 (2CH), 76.9 (CH), 76.6 (CH), 73.8 (2CH), 73.1 (CH), 73.0 (CH), 72.1 (2CH), 71.7 (2CH), 70.7 (CH), 70.2 (CH), 69.9 (CH), 69.5 (CH), 67.8 (CH), 62.5 ($2CH_2$), 61.9 (CH_2), 61.6 (CH_2), 52.5 (CH_3), 52.34(CH_3), 20.91($2CH_3$), 20.79($4CH_3$), 20.66($8CH_3$); **HR-MS (ESI)**: for $C_{34}H_{42}O_{19}S$ (M + Na)$^+$: *m/z* calcd 809.1939, found 809.1940.

Compounds β–3l and α–3l:

Following the general procedure of coupling, a mixture of (2R,3S,4R,5R,6S)-5-acetamido-2-(acetoxymethyl)-6-mercaptotetrahydro-2H-pyran-3,4-diyl diacetate **1d** (200 mg, 0.54 mmol) and methyl 2-iodobenzoate **2a** (96 mg, 0.36 mmol) was heated for 1 h. The residue was purified by flash chromatography over silica gel (Cyclohexane: ethyl acetate 2:8) to afford products **β–3l** (109 mg, 0.22 mmol, 60%) and **α–3l** (66.6 mg, 0.133 mmol, 37%).

(2R,3S,4R,5R,6S)-5-acetamido-2-(acetoxymethyl)-6-((2-(methoxycarbonyl)phenyl)thio)tetrahydro-2H-pyran-3,4-diyl diacetate (β–3l)

Dark yellow solid; **mp** (152-153 °C); TLC: R_f = 0.25 (Cyclohexane: ethyl acetate 2:8); **IR** (thin film, neat) vmax/cm^{-1}: 1746, 1716, 1685, 1666, 1541, 1469, 1435, 1380, 1366, 1295, 1254, 1229, 1214, 1146, 1113, 1089, 1040, 912, 749; **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm): 7.82 (dd, *J* = 7.7, 1.6 Hz, 1H, H_{arom}), 7.63 (d, *J* = 7.9 Hz, 1H, H_{arom}), 7.43 (td, *J* = 7.7, 1.5 Hz, 1H, H_{arom}), 7.32 (td, *J* = 7.5, 1.0 Hz, 1H, H_{arom}), 5.95 (d, *J* = 8.7 Hz, 1H, NH), 5.40 (t, *J* = 9.7 Hz, 1H, $H_{3'}$), 5.15(d, *J* = 9.0 Hz, 1H, $H_{1',anom}$), 5.07 (t, *J* = 10.0 Hz, 1H, $H_{4'}$), 4.26 – 4.08 (m, 2H, $H_{6'}$), 3.95 (m, 1H, $H_{2'}$), 3.89 (s, 3H, CO_2Me), 3.81 – 3.72 (m, 1H, $H_{5'}$), 2.06 (s, 3H, OAc), 2.02 (s, 6H, OAc), 1.94 (s, 3H, NAc); **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm): 170.4 (C=O), 170.3 (C=O), 170.1 (C=O), 169.2 (C=O), 167.2 (C=O), 134.7($C_{IV.arom}$), 132.0 ($C_{VI.arom}$),131.9 ($CH_{III.arom}$), 131.7 ($CH_{III.arom}$), 130.1 ($CH_{III.arom}$), 126.8 ($CH_{III.arom}$), 84.6 (CH_{anom}), 75.4 (CH, $C_{5'}$), 73.2 (CH, $C_{3'}$), 68.3 (CH, $C_{4'}$), 62.1 (CH_2, $C_{6'}$), 53.6 (CH, $C_{2'}$), 52.1 (CH_3, CO_2Me), 23.0 (NHC(O)$\underline{CH_3}$), 20.4 (2 C(O)$\underline{CH_3}$), 20.3 (C(O)$\underline{CH_3}$); **HR-MS (ESI)**: for $C_{22}H_{27}NO_{10}S$ (M + Na)$^+$: *m/z* calcd 520.1253, found 520.1253.

(2R,3S,4R,5R,6R)-5-acetamido-2-(acetoxymethyl)-6-((2-(methoxycarbonyl)phenyl)thio)tetrahydro-2H-pyran-3,4-diyl diacetate (α–3l).

Light yellow solid; **mp** (212-213 °C); TLC: R_f = 0.4 (Cyclohexane: ethyl acetate 2:8); **IR** (thin film, neat) ν_{max}/cm^{-1}: 1744, 1721, 1657, 1535, 1467,1435, 1368, 1250, 1238, 1217, 1143, 1107, 1031, 915, 832, 744, 689; **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm): 7.93 (dd, J_1 = 7.8 Hz, J_1 = 1.5 Hz, 1H, H_{arom}), 7.69 (d, *J* = 7.4 Hz, 1H, H_{arom}), 7.47 (t, J_1 = 9.0 Hz, J_2 = 2.0 Hz, 1H, 1H, H_{arom}), 7.32 – 7.24 (m, 1H, H_{arom}), 6.05 (d, *J* = 8.8 Hz, 1H, NH), 5.80 (d, *J* = 5.5 Hz, 1H, $H_{1'anom}$), 5.34 – 5.13 (m, 2H, $H_{3' \text{ and } 4'}$), 4.69 (dd, *J* = 10.9, 5.5 Hz, 1H, $H_{2'}$), 4.50 – 4.39 (m, 1H, $H_{5'}$), 4.28 (dd, J

= 12.4, 4.5 Hz, 1H, $H_{6'}$), 4.05 (d, *J* = 10.2 Hz, 1H, $H_{6'}$), 3.94 (s, 3H, CO_2Me), 2.05 (s, 3H, OAc), 2.04 (m, 6H, OAc), 1.95 (s, 3H, NHAc); **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm): 171.1 (C=O), 170.3 (C=O), 169.9 (C=O), 169.1 (C=O), 166.6 (C=O), 136.8 ($C_{IV.arom}$), 132.6 (CH_{arom}), 130.8 (CH_{arom}), 129.2 ($C_{IV.arom}$), 128.8 (CH_{arom}), 125.8 (CH_{arom}), 84.7 (CH_{anom}), 71.0 (CH, $C_{3'}$), 68.9 (CH, $C_{5'}$), 67.9 (CH, $C_{4'}$), 61.6 (CH_2, $C_{6'}$), 52.3 (CH, $C_{2'}$), 52.1 (CH_3, CO_2Me), 22.9 (CH_3, COMe), 20.4 ($2CH_3$, COMe), 20.3 (CH_3, NHMe); **HR-MS (ESI)**: for $C_{22}H_{27}NO_{10}S$ (M + Na)$^+$: *m/z* calcd 520.1253, found 520.1261.

Compounds β–3m and α–3m:

Following the general procedure of coupling, a mixture of (2R,3S,4R,5R,6S)-5-acetamido-2-(acetoxymethyl)-6-mercaptotetrahydro-2H-pyran-3,4-diyl diacetate **1f** (200 mg, 0.55mmol) and methyl 2-iodo-5-methylbenzoate **2b** (99.5 mg, 0.366 mmol) was heated for overnight(12 hrs. The residue was purified by flash chromatography over silica gel (Cyclohexane:ethyl acetate 2:8) to afford the products **β–3m** (52 mg, 0.13 mmol, 37%) and **α–3m** (44 mg, 0.08 mmol, 31%).

(2R,3S,4R,5R,6S)-5-acetamido-2-(acetoxymethyl)-6-((2-(methoxycarbonyl)-4-methylphenyl)thio)tetrahydro-2H-pyran-3,4-diyl diacetate (β–3m)

Light yellow solid; **mp** (209 - 210°C); TLC: R_f = 0.25 (Cyclohexane: ethyl acetate 2:8); **IR** (thin film, neat) ν_{max}/cm^{-1}: 1744, 1725, 1658, 1528, 1474, 1434, 1370, 1302, 1245, 1207, 1109, 1032, 980, 916, 819, 783, 766, 749, 641 ; **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm):7.59 (d, *J* = 1.6 Hz, 1H), 7.52 (d, *J* = 8.1 Hz, 1H), 7.21 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.16 (d, *J* = 8.6 Hz, 1H), 5.34 (dd, *J* = 20.7, 10.8 Hz, 1H), 5.13 – 4.96 (m, 2H), 4.15 (ddd, J = 14.6, 12.2, 3.9 Hz, 2H), 3.93 (d, *J* = 8.7 Hz, 1H), 3.71 (dd, *J* = 8.9, 6.5 Hz, 1H), 2.35 (s, 3H), 2.05 (s, 3H), 2.00 (d, *J* = 3.0 Hz, 6H), 1.93 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm): 171.2 (C=O), 171.1 (C=O), 171.0 (C=O), 170.0 (C=O), 168.3 (C=O), 138.2 (C), 133.8 (CH), 133.4 (C), 133.2 (CH), 131.3 (CH), 131.1 (C), 85.8 (CH), 76.1 (CH), 74.2 (CH), 69.1 (CH), 62.9 (CH_2), 54.3 (CH), 52.9 (CH_3), 23.8 (CH_3), 21.4 (CH_3), 21.3 (CH_3), 21.3 (CH_3), 21.14(CH_3); **HR-MS (ESI)**: for $C_{23}H_{29}NO_{10}S$ (M + Na)$^+$: *m/z* calcd 534.1410, found 534.1433.

(2R,3S,4R,5R,6R)-5-acetamido-2-(acetoxymethyl)-6-((2-(methoxycarbonyl)-4-methylphenyl)thio)tetrahydro-2H-pyran-3,4-diyl diacetate (α–3m)

Beige solid; **mp** (83-84°C);TLC: R_f = 0.46 (Cyclohexane: ethyl acetate 2:8); **IR** (thin film, neat) ν_{max}/cm^{-1}:2956, 2923, 2853, 1745, 1715, 1684, 1666, 1539, 1475, 1435, 1378, 1366, 1300, 1249, 1228, 1207, 1115, 1087, 1036, 977, 913, 824, 785, 735, 701, 645 ; **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm):7.71 (s, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.26 (d, *J* = 7.1 Hz, 1H), 6.07 (d, *J* = 8.9 Hz, 1H), 5.71 (d, *J* = 5.4 Hz, 1H), 5.33 – 5.07 (m, 2H), 4.74 – 4.57 (m, 1H), 4.44 (d, *J* = 6.2 Hz, 1H), 4.27 (dd, *J* = 12.4, 4.4 Hz, 1H), 4.03 (dd, *J* = 12.3, 1.7 Hz, 1H), 3.91 (s, 3H), 2.34 (s, 3H), 2.03 (d, *J* = 1.2 Hz, 9H), 1.94 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm):171.31(C=O), 170.5 (C=O), 170.0 (C=O), 169.5(C=O), 167.0 (C=O), 136.5 (C), 133.5 (CH), 133.0 (C), 131.5 (CH), 130.0 (C), 130.0 (CH), 86.0 (CH), 71.5 (CH), 69.0 (CH), 68.0 (CH), 62.0 (CH_2), 52.5 (CH), 52.0 (CH_3), 30.5 (CH_3), 23.0 (CH_3), 21.0 ($2CH_3$), 21.0 (CH_3); **HR-MS (ESI)**: for $C_{23}H_{29}NO_{10}S$(M + Na)$^+$: *m/z* calcd 534.1410, found 534.1396.

Typical procedure for cyclization of thioglycosides (3a-m) into fused thioglycosyl benzoxathiepinones and benzothiapinones of type (4).

A mixture of thioglycosides **(3a-m)** (1 equiv) and K_2CO_3 (0.3 equiv) in methanol (0.1M) were placed in a small ballon and the mixture was stirred under argon at room temperature for 30 min. The crude mixture was then filtered through celite and washed with 10 mL of methanol and filtered during only 1 min. The filtrate was concentrated under reduced pressure by rotavap at 25 °C for (1-2 h).

(2R,3S,4S,4aR,11aS)-3,4-dihydroxy-2-(hydroxymethyl)-2,3,4,4a-tetrahydrobenzo[e]pyrano[3,2-b][1,4]oxathiepin-6(11aH)-one (4a).

Following the general procedure of cyclization by mixing **3a** (50 mg, 0.1 mmol) with (4.5 mg, 0.03 mmol) of K_2CO_3 in a small ballon (50 ml.) under argon at RT for 30 min. The residue was filtered through celite with methanol for 1 min, the solvent then evaporated by rotavap at (25 °C) for (1-2 h) without purification by flash column chromatography affording the desired product **4a** (29 mg, 0.98 mmol, 98%) as a light yellow solid; **mp** (206-207 °C); TLC: R_f = 0.62 (DCM: MeOH 85: 15); **IR** (thin film, neat) ν_{max}/cm^{-1}: 2835, 1701, 1646, 1449, 1402, 1317, 1259,1118, 1085, 1012, 748; **^{1}H NMR** (300 MHz, $MeOD_4$) δ (ppm): 7.88 (d, *J* = 1.5 Hz, 1H, H_{arom}), 7.76 (dd, *J* = 8.1, 0.8 Hz, 1H, H_{arom}), 7.51 (td, *J* = 9.0, 1.5 Hz, 1H, H_{arom}), 7.27 (td, *J* = 7.7, 1.1 Hz, 1H, H_{arom}), 4.76 (d, *J* = 9.6 Hz, 1H, $H_{1',anom}$), 3.95 – 3.85 (m, 1H, $H_{6'}$), 3.69 (dd, *J* = 12.1, 5.6 Hz, 1H, $H_{6'}$), 3.50 – 3.37 (m, 4H, $H_{2', 3', 4', 5'}$); **^{13}C NMR** (75 MHz, $MeOD_4$) δ (ppm): 168.9 (C=O $_{lactone}$), 139.9 ($C_{IV.arom}$), 133.7 (CH_{arom}), 131.5 (CH_{arom}), 130.7 ($C_{IV.arom}$), 130.1 (CH_{arom}), 126.5 (CH_{arom}), 87.5 (CH, $C_{1',anom}$), 81.9 (CH, $C_{3'}$), 79.8 (CH, $C_{4'}$), 73.9 (CH, $C_{2'}$), 71.4 (CH, $C_{5'}$), 62.8 (CH_2, $C_{6'}$); **HR-MS** (**APCI negative)** *m/z*: for $C_{13}H_{14}O_6S$ (M – H$^+$): m/z calcd 297.0438, found 297.0433.

(2R,3S,4S,4aR,11aS)-3,4-dihydroxy-2-(hydroxymethyl)-8-methyl-2,3,4,4a-tetrahydrobenzo[e]pyrano[3,2-b][1,4]oxathiepin-6(11aH)-one (4b).

Following the general procedure of cyclization by mixing **3b** (50 mg, 0.097 mmol) with (4.0 mg, 0.03 mmol) of K_2CO_3 in a small ballon (50 ml.) under argon at RT for 30 min. The residue was filtered through celite with methanol for 1 min, the solvent then evaporated by rotavap at (25 °C) for (1-2 hr.) without purification by flash column chromatography affording the desired product **4b** (31 mg, 0.096 mmol, 99%) as a yellow solid; **mp** (202-203 °C); TLC: R_f = 0.57 (DCM: MeOH 85 : 15); **IR** (thin film, neat) ν_{max}/cm^{-1}: 2834, 1397, 1622, 1391, 1367, 1312, 1256, 1214, 1115, 1022, 1014, 831, 704; **^{1}H NMR** (300 MHz, $MeOD_4$): 7.63 (d, *J* = 8.3 Hz, 2H), 7.32 (dd, *J* = 8.5, 1.8 Hz, 1H), 4.66 (d, *J* = 9.6 Hz, 1H), 3.95 – 3.78 (m, 1H), 3.78 – 3.34 (m, 4H), 3.26 (d, *J* = 8.5 Hz, 1H),2.32 (s, 3H); **^{13}C NMR** (75 MHz, $MeOD_4$) δ (ppm): 169.1 (C=O), 137.1 (C), 135.6 (C), 134.4 (CH), 131.8 (CH), 131.4 (C), 130.9 (CH), 87.7 (CH), 81.9(CH), 79.7 (CH), 73.8 (CH), 71.3 (CH), 62.8

(CH_2), 20.7 (CH_3); **HR-MS** (**APCI negative)** *m/z*: for $C_{14}H_{16}O_6S$(M – H^+): m/z calcd 311.0595, found 311.0589.

(2R,3S,4S,4aR,11aS)-3,4-dihydroxy-2-(hydroxymethyl)-8,9-dimethyl-2,3,4,4a-tetrahydrobenzo[e]pyrano[3,2-b][1,4]oxathiepin-6(11aH)-one (4c).

Following the general procedure of cyclization by mixing (50 mg, 0.094 mmol)of **3c** with (4.0 mg, 0.03mmol) of K_2CO_3 in a small ballon (50 ml.) under argon at RT for 30 min.The residue was filtered through celite with methanol for 1 min, the solvent then evaporated by rotavap at (25 °C) for (1-2 hrs.) without purification by flash column chromatography affording the desired product **4c** (27 mg, 0.08 mmol, 87%)as a yellow solid; **mp** (181-182°C); TLC: $\mathbf{R_f}$ = 0.6 (DCM: MeOH 85:15); **IR** (thin film, neat) ν_{max}/cm^{-1}: 2918, 2850, 1701, 1631, 1488, 1400, 1361, 1311, 1287, 1260, 1233, 1189, 1163, 1124, 1074, 1021, 936, 875, 831, 782, 734, 703, 617; **^{1}H NMR** (300 MHz, $MeOD_4$): 7.59 (d, *J* = 20.2 Hz, 2H), 4.66 (d, *J* = 9.6 Hz, 1H), 3.93 – 3.81 (m, 1H), 3.63 (dd, *J* = 12.1, 6.3 Hz, 4H), 3.57 – 3.33 (m, 1H), 2.29 (s, 3H), 2.24 (s, 3H); **^{13}C NMR** (75 MHz, $MeOD_4$) δ (ppm): 169.0 (C=O), 143.5 (C), 136.5 (C), 135.5 (C), 132.5 (CH), 131.6 (CH), 128.3 (C), 87.75(CH), 82.2 (CH), 79.8 (CH), 73.9 (CH), 71.5 (CH), 62.9 (CH_2), 20.1 (CH_3), 19.1 (CH_3); **HR-MS**(**APCI negative)** *m/z*: for $C_{15}H_{18}O_6S$ (M - H^+) m/z calcd 325.0751, found 325.0746.

(2R,3S,4S,4aR,11aS)-9-chloro-3,4-dihydroxy-2-(hydroxymethyl)-2,3,4,4a-tetrahydrobenzo[e]pyrano[3,2-b][1,4]oxathiepin-6(11aH)-one (4d).

Following the general procedure of cyclization by mixing (50 mg, 0.093 mmol) of **3d** with (4.0 mg, 0.03 mmol) of K_2CO_3 in a small ballon (50 ml.) under argon at RT for 30 min. The residue was filtered through celite with methanol for 1 min, the solvent then evaporated by rotavap at (25 °C) for (1-2 h.) without purification by flash column chromatography affording the desired product **4d** (30.5 mg, 0.09 mmol, 97%) as a light yellow solid; **mp** (182-183 °C); TLC: $\mathbf{R_f}$= 0.54 (DCM: MeOH 85:15); **IR** (thin film, neat) ν_{max}/cm^{-1} :2834, 1684, 1576, 1546, 1467, 1326, 1259, 1154, 1112, 1075, 1031, 1014, 879, 811, 781; **^{1}H NMR** (300 MHz, $MeOD_4$) δ (ppm): 7.85 (d, J = 8.4 Hz, 1H), 7.75 (s, 1H), 7.24 (d, *J* = 10.5 Hz, 1H), 4.74 (d, *J* = 9.5 Hz, 1H), 3.86 (t, *J* = 10.2 Hz, 1H), 3.65 (d, *J* = 6.3 Hz, 1H), 3.39 (d, *J* = 26.4 Hz, 4H); **^{13}C NMR** (75 MHz, $MeOD_4$) δ (ppm): 167.8 (C=O),143.2 (C), 140.0 (C), 133.1 (CH), 129.1 (CH), 128.3 (C), 126.3 (CH), 87.0 (CH), 82.1 (CH), 79.8 (CH), 73.9 (CH), 71.3 (CH), 62.7 (CH_2); **HR-MS** (**APCI negative)** m/z: for $C_{13}H_{13}ClO_6S$ (M -H^+): m/z calcd 331.0049, found.

(2R,3S,4S,4aR,11aS)-8-bromo-3,4-dihydroxy-2-(hydroxymethyl)-2,3,4,4a-tetrahydrobenzo[e]pyrano[3,2-b][1,4]oxathiepin-6(11aH)-one (4e).

Following the general procedure of cyclization by mixing (50 mg, 0.086 mmol) of **3e** with (3.6 mg, 0.025 mmol) of K_2CO_3 in a small ballon (50 ml.) under argon at RT for 30 min. The residue was filtered through celite with methanol for 1 min, the solvent then evaporated by rotavap at (25 °C) for (1-2 h.) without purification by flash column chromatography affording the desired product **4e**(32 mg, 0.084 mmol, 98%) as a yellow solid; **mp**(205-206°C); TLC: $\mathbf{R_f}$= 0.5 (DCM: MeOH 85: 15); **IR** (thin film, neat) ν_{max}/cm^{-1}: 2918, 1704, 1652,1457, 1311, 1248, 1082, 934, 832, 811, 780 ; **^{1}H NMR** (300 MHz, $MeOD_4$) δ (ppm):7.98 (dd, *J* = 1.8, 0.7 Hz, 1H), 7.63 (d, *J* = 2.0 Hz, 2H),4.73 (d, *J* = 9.5 Hz, 1H), 3.88 (dd, *J* = 12.1, 2.0 Hz, 1H), 3.65 (dd, *J* = 12.1, 5.8 Hz, 1H), 3.54 – 3.35 (m, 3H), 3.32 (d, *J* = 4.5 Hz, 1H); **^{13}C NMR** (75 MHz, $MeOD_4$) δ (ppm): 147.5 (C=O), 139.9 (C), 136.4 (CH), 134.1 (CH), 132.0 (C), 131.6 (CH), 119.6 (C), 87.1 (CH), 82.0 (CH), 79.7 (CH), 73.9 (CH), 71.3 (CH), 62.8 (CH_2); **HR-MS**(**APCI negative)** m/z: for $C_{13}H_{13}BrO_6S$ (M - H^+): m/z calcd 374.9543 (^{79}Br), 376.9524 (^{81}Br),found 374.9529 (^{79}Br), 376.9514 (^{81}Br).

(2R,3S,4S,4aR,11aS) – methyl 3 , 4 – dihydroxy – 2 -(hydroxymethyl)-6-oxo-2,3,4,4a,6,11a-hexahydrobenzo[e]pyrano[3,2-b][1,4]oxathiepine-9-carboxylate (4f).

Following the general procedure of cyclization by mixing (50 mg, 0.089 mmol) of **3f** with (4.0 mg, 0.03 mmol) of K_2CO_3 in a small ballon (50 ml.) under argon at RT for 30 min. The residue was filtered through celite with methanol for 1 min, the solvent then evaporated by rotavap at (25 °C) for (1-2 h.) without purification by flash column chromatography affording the desired product **4f** (28 mg, 0.089 mmol, 99%) as a white to light beige solid; TLC: $\mathbf{R_f}$= 0.47 (DCM: MeOH 85:15); **IR** (thin film, neat) ν_{max}/cm^{-1}: 2957, 2919, 2851, 1728, 1650, 1558, 1476, 1434, 1384, 1313, 1290, 1259, 1192, 1119, 1060, 1034, 913, 828, 747, 670, 653; **^{1}H NMR** (300 MHz, $MeOD_4$) δ (ppm): 8.40 (s, 1H), 7.93 (d, *J* = 8.1 Hz, 1H), 7.84 (d, *J* = 6.6 Hz, 1H), 4.76 (d, *J* = 9.4 Hz, 1H), 3.95 – 3.85 (m, 1H), 3.74 (dd, *J* = 13.1, 2.7 Hz, 1H), 3.50 – 3.35 (m, 4H), 1.27 (s, 3H); **^{13}C NMR** (75 MHz, $MeOD_4$) δ (ppm): 168.0 (C=O), 167.4 (C=O), 140.9 (C), 134.7 (C), 134.2 (C), 131.6 (CH), 130.8 (CH), 126.9 (CH), 87.5 (CH), 82.1 (CH), 79.8 (CH), 73.8 (CH), 71.0(CH), 62.5 (CH_2), 30.8 (CH_3); **HR-MS**(**APCI negative)** m/z: for $C_{15}H_{16}O_8S$ (M - H^+): m/z calcd 355.0493, found 355.0488.

(5aS,7R,8S,9S,9aR)-8,9-dihydroxy-7-(hydroxymethyl)-7,8,9,9a-tetrahydropyrano[3,2-b][1,4]oxathiepin-2(5aH)-one (4g).

Following the general procedure of cyclization by mixing of **3g** (50 mg, 0.1 mmol) with (5.0 mg, 0.03mmol) of K_2CO_3 in a small ballon (50 ml.) under argon at RT for 30 min.The residue was filtered through celite with methanol for 1 min, the solvent then evaporated by rotavap at (25 °C) for (1-2 h.) without purification by flash column chromatography affording the desired product **4g** (27 mg, 0.98 mmol, 98%) as a light yellow solid; **mp** (184-185 °C); TLC: $\mathbf{R_f}$ = 0.43 (DCM: MeOH 85:15); **IR** (thin film, neat) ν_{max}/cm^{-1}: 1684, 1623, 1575, 1371, 1312, 1252, 1183, 1086, 1051, 1026, 830, 803, 759; **^{1}H NMR** (300 MHz, $MeOD_4$) δ (ppm):7.55 (d, *J* = 10.3 Hz, 1H), 5.93 (d, J = 10.2 Hz, 1H), 4.50 (d, *J* = 9.4 Hz, 1H), 3.86 (dd, *J* = 12.0, 1.5 Hz, 1H), 3.66 (dd, *J* = 12.1, 5.1 Hz, 1H), 3.41 – 3.31 (m, 4H); **^{13}C NMR** (75 MHz, $MeOD_4$) δ (ppm): 168.7 (C=O), 148.2 (CH), 113.8 (CH), 87.4(CH), 82.5 (CH), 79.4 (CH), 74.5 (CH), 71.2 (CH), 62.7 (CH_2); **HR-MS**(**APCI negative)** *m/z*: for $C_9H_{12}O_6S$ (M - H^+): m/z calcd 247.0282, found 247.0273.

(2R,3R,4S,4aR,11aS)-3,4-dihydroxy-2-(hydroxymethyl)-2,3,4,4a-tetrahydrobenzo[e]pyrano[3,2-b][1,4]oxathiepin-6(11aH)-one (4h).

Following the general procedure of cyclization by mixing (50 mg, 0.1 mmol) of **3h** with (4.5 mg, 0.03 mmol) of K_2CO_3 in a small ballon (50 ml.) under argon at RT for 30 mins. The residue was filtered through celite with methanol for 1 min, the solvent then evaporated by rotavap at (25 °C) for (1-2 hrs.) without purification by flash column chromatography affording the desired product **4h** (29 mg, 0.097 mmol, 97%)as a white to light yellow solid; **mp** (190-192 °C); TLC: R_f = 0.35 (DCM: MeOH 85:15); **IR** (thin film, neat) ν_{max}/cm^{-1}: 2939, 1704, 1646, 1448,1401, 1314, 1258, 1086, 1022, 866, 748; **^{1}H NMR** (300 MHz, $MeOD_4$) δ (ppm): 7.85 (dd, J = 7.8, 1.5 Hz, 1H), 7.78 (dd, J = 8.2, 0.8 Hz, 1H), 7.53 – 7.43 (m, 1H), 7.24 (td, *J* = 7.8, 1.1 Hz, 1H), 4.70 (d, *J* = 9.7 Hz, 1H), 3.92 (d, *J* = 3.2 Hz, 1H), 3.82 – 3.62 (m, 4H), 3.53 (dd, *J* = 9.1, 3.3 Hz, 1H); **^{13}C NMR** (75 MHz, $MeOD_4$) δ (ppm):163.9 (C=O), 140.7 (C), 133.70 (CH), 131.6 (CH), 130.3 (C), 129.7 (CH), 126.2 (CH), 88.1 (CH), 80.6 (CH), 76.4 (CH), 70.9 (CH), 70.5 (CH), 62.7 (CH_2); **HR-MS** (**APCI negative)** m/z: for $C_{13}H_{14}O_6S$ (M - H^+): m/z calcd 297.0438, found 297.0434.

(2R,3R,4S,4aR,11aS)-3,4-dihydroxy-2-(hydroxymethyl)-8-methyl-2,3,4,4a-tetrahydrobenzo[e]pyrano[3,2-b][1,4]oxathiepin-6(11aH)-one (4i).

Following the general procedure of cyclization by mixing (40 mg, 0.075 mmol) of **3i** with (1.1 mg, 0.03 mmol) of K_2CO_3 in a small ballon under argon at RT for 30 min.The residue was filtered through celite with methanol for 1 min, the solvent then evaporated by rotavap at (25 °C) for (1-2 h.) without purification by flash column chromatography affording the desired product **4i** (22 mg, 0.072 mmol, 97%) as a light yellow solid; **mp** (205-206 °C); TLC: R_f = 0.45 (DCM: MeOH 85:15); **IR** (thin film, neat) ν_{max}/cm^{-1} : 2945 ,2833 , 1700, 1623, 1398, 1369, 1306, 1025, 1007, 977, 831, 703 ; **^{1}H NMR** (300 MHz, $MeOD_4$) δ (ppm):7.71 – 7.53 (m, 2H), 7.27 (dd, *J* = 8.3, 1.5 Hz, 1H), 4.62 (d, *J* = 9.7 Hz, 1H), 3.88 (d, *J* = 2.8 Hz, 1H), 3.77 – 3.56 (m, 4H), 3.50 (dd, *J* = 9.1, 3.3 Hz, 1H), 2.28 (s, 3H); **^{13}C NMR** (75 MHz, $MeOD_4$) δ (ppm): 169.0 (C=O), 136.7 (C), 136.5 (C), 134.5 (CH), 131.9 (CH), 130.7 (C), 130.4 (CH), 88.4 (CH), 80.5 (CH), 76.3 (CH), 70.9 (CH), 70.5 (CH), 62.7 (CH_2),20.6 (CH_3); **HR-MS**(**APCI negative)** *m/z*: for $C_{14}H_{16}O_6S$ (M -H^+): m/z calcd 311.0595, found 311.0589.

(2R,3R,4S,4aR,11aS)-8-bromo-3,4-dihydroxy-2-(hydroxymethyl)-2,3,4,4a-tetrahydrobenzo[e]pyrano[3,2-b][1,4]oxathiepin-6(11aH)-one (4j).

Following the general procedure of cyclization by mixing (50 mg, 0.086 mmol) **3j** with (3.0 mg, 0.02 mmol) of K_2CO_3 in a small ballon (50 ml.) under argon at RT for 30 min. The residue was filtered through celite with methanol for 1 min, the solvent then evaporated by rotavap at (25 °C) for (1-2 h.) without purification by flash column chromatography affording the desired product **4j** (31 mg ,0.082 mmol, 96%) as a light yellow solid; **mp** (208-209 °C); TLC: R_f = 0.54 (DCM: MeOH 85:15); **IR** (thin film, neat) ν_{max}/cm^{-1}: 2948, 2835, 1711, 1451, 1394, 1368, 1312, 1250, 1081, 1025, 1009, 830, 703; **^{1}H NMR** (300 MHz, $MeOD_4$) δ (ppm): 7.97 (d, *J* = 2.2 Hz, 1H), 7.69 (d, J = 8.7 Hz, 1H), 7.61 (dd, *J* = 8.7, 2.3 Hz, 1H), 4.70 (d, *J* = 9.7 Hz, 1H), 3.92 (d, *J* = 3.3 Hz, 1H), 3.81 – 3.63 (m, 4H), 3.54 (dd, *J* = 9.1, 3.3 Hz, 1H); **^{13}C NMR** (75 MHz, $MeOD_4$) δ (ppm): 167.5 (C=O), 140.6 (C), 136.7 (CH), 134.4 (CH), 131.9 (C), 131.7 (CH), 119.7 (C), 87.9 (CH), 80.9 (CH), 76.6 (CH), 71.1 (CH), 70.7 (CH), 63.0(CH_2); **HR-MS**(**APCI negative)** *m/z*: for $C_{13}H_{13}BrO_6S$ (M - H^+): m/z calcd 374.9543 (^{79}Br), 376.9539 (^{81}Br),found 374.9529 (^{79}Br), 376.9520 (^{81}Br).

(2R,3S,4S,4aR,11aS)-4-hydroxy-2-(hydroxymethyl)-3-(((2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-2,3,4,4a-tetrahydrobenzo[e]pyrano[3,2-b][1,4]oxathiepin-6(11aH)-one (4k).

Following the general procedure of cyclization by mixing (50 mg, 0.06 mmol) **3m** with (3.0 mg, 0.02 mmol) of K_2CO_3 in a small ballon (50 ml.) under argon at RT for 24 h. The residue was filtered through celite with methanol for 1 min, the solvent then evaporated by rotavap at (25 °C) for (1-2 h.) then purification by flash column chromatography affording the desired product **4m** (29 mg, 0.06 mmol, 98%) as a colorless oily mixture of α,β anomers (24:76); TLC: R_f = 0.16 (DCM: MeOH 85:15); **IR** (thin film, neat) ν_{max}/cm^{-1}: 1701, 1436, 1310, 1256, 1078, 1020, 830, 743, 670, 653; **^{1}H NMR** (300 MHz, $MeOD_4$) δ (ppm): ^{1}H NMR (300 MHz, MeOD) δ 7.90 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.72-7.74 (m, 2H), 7.49-7.52 (m, 2H), 7.20-7.30 (m, 3H), 5.66 (d, *J* = 5.3 Hz, 1H), 4.84 (d, *J* = 9.8 Hz, 1H), 4.56 (d, *J* = 9.6 Hz, 1H), 4.32-4.51 (m, 2H), 4.0-3.8 (m, 6H), 3.81-3.40 (m, 5H); **^{13}C NMR** (75 MHz, $MeOD_4$) δ (ppm): ^{13}C NMR (75 MHz, MeOD) δ 167.4, 160.7, 138.3, 132.3, 132.0, 130.2, 130.0, 129.6, 129.4, 128.6, 125.3, 125.1, 103.2, 103.1, 86.9, 85.7, 79.2, 79.0, 78.6, 76.7, 76.5, 76.4, 73.5, 72.7, 72.26, 71.9, 71.7, 69.9, 61.0, 60.4, 60.1, 51.4; **HR-MS**(**APCI negative)** *m/z*: for $C_{19}H_{24}O_{11}S$ (M - H^+): m/z calcd 459.0967, found 459.0923.

(2R,3S,4R)-5-acetyl-3,4-dihydroxy-2-(hydroxymethyl)-3,4,4a,5-tetrahydro-2H-benzo[f]pyrano[2,3-b][1,4]thiazepin-6(11aH)-one (4m).

Following the general procedure of cyclization by mixing (50 mg, 0.1 mmol) of **3m** with (14 mg, 0.1 mmol) of K_2CO_3 in a small ballon (50 ml.) under argon at RT for 24 h., the residue was filtered through celite with methanol for 1 min, the solvent then evaporated by rotavap at (25 °C) for (1-2 hrs.) then purification by flash column chromatography affording the desired product **4m** (31 mg, 0.098 mmol, 98%)as a white to light yellow solid; **mp** (215-216 °C); TLC: R_f = 0.32 (DCM: MeOH9:1); **IR** (thin film, neat) ν_{max}/cm^{-1}: 2988, 2960, 2327, 1680, 1452, 1314, 1060, 1034, 892, 869, 777, 670 ; **^{1}H NMR** (300 MHz, $MeOD_4$) δ (ppm): 7.68 (d, J = 7.8 Hz, 2H, H_{arom}), 7.44 – 7.30 (td, *J* = 9.0, 1.1 Hz, 1H, H_{arom}), 7.18 (td, *J* = 8.6, 1.1 Hz, 1H, H_{arom}), 5.70 (d, *J* = 5.3 Hz, 1H, $H_{1',anom}$), 4.04 (dd, *J* = 11.2, 5.3 Hz, 1H, $H_{2'}$), 3.92 (dd, J = 8.5, 5.0 Hz, 1H, $H_{5'}$), 3.64-3.67 (m, 2H, $H_{6',5'}$), 3.60 – 3.27 (m, 2H, $H_{4',6'}$), 1.85 (s, 3H, NHAc); **^{13}C NMR** (75 MHz, $MeOD_4$) δ (ppm): 173.8 (C=O, $C_{lactame}$), 168.9 (C=O, NAc), 138.4 (C_{IVarom}), 133.3 (CH_{arom}), 132.8 (C_{IVarom}), 131.8 (CH_{arom}), 131.2 (CH_{arom}), 127.2 (CH_{arom}), 87.3 (CH, $C_{1',anom}$), 75.2 (CH, $C_{5'}$), 72.6 (CH, $C_{3'}$), 72.4 (CH, $C_{4'}$), 62.4 (CH_2, $C_{6'}$),

56.2 (CH, $C_{2'}$), 22.6 (CH_3, NHAc); **HR-MS(APCI negative)** *m/z*: for $C_{15}H_{17}NO_6S$ (M - H^+): m/z calcd 338.0704, found 338.0718.

(2R,3S,4R,4aR,11aS)-5-acetyl-3,4-dihydroxy-2-(hydroxymethyl)-8-methyl-3,4,4a,5-tetrahydro-2H-benzo[f]pyrano[2,3-b][1,4]thiazepin-6(11aH)-one(4n).

Following the general procedure of cyclization by mixing (50 mg, 0.097 mmol) **3n** with (13.5 mg, 0.097 mmol) of K_2CO_3 in a small ballon (50 ml.) under argon at RT for 72 h., the residue was filtered through celite with methanol for 1 min, the solvent then evaporated by rotavap at (25 °C) for (1-2 h.), then purification by flash column chromatography affording the desired product **4n** (18 mg, 0.05 mmol, 52%) as a white solid; **mp** (225-226°C) ;TLC: R_f = 0.3(DCM: MeOH 85:15); **IR** (thin film, neat) ν_{max}/cm^{-1}: 2957, 2922, 2852, 2360, 1704, 1657, 1538, 1461, 1376, 1315, 1287, 1252, 1213, 1119, 1087, 1054, 996, 953, 913, 858, 815, 782, 722, 672, 644,62; **^{1}H NMR** (400 MHz, $DMSO_{4}$-d_6) δ (ppm): 7.61 (s, 1H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 4.77 (d, *J* = 10.5 Hz, 1H), 3.78 (s, 1H), 3.72 – 3.59 (m, 3H), 3.20 (d, *J* = 33.6 Hz, 2H), 2.28 (s, 3H), 1.79 (s, 3H); **^{13}C NMR** (101 MHz, $DMSO_{4}$-d_6) δ (ppm): 166.6 (C=O), 163.7 (C=O), 135.9 (C), 134.7 (C), 133.6 (CH), 130.5 (CH), 128.7 (C), 128.0 (CH), 84.5 (CH), 81.1 (CH), 75.7 (CH), 70.4 (CH), 61.1 (CH_2), 54.4 (CH), 23.2 (CH_3), 20.2 (CH_3); **HR-MS(APCI negative)** *m/z*: for $C_{16}H_{19}NO_6S$ (M - H^+): m/z calcd 352.0860, found 352.0871.

(2R,3S,4S,4aR,11S,11aS)-3,4-dihydroxy-2-(hydroxymethyl)-3,4,4a,11a-tetrahydro-2H,6H-benzo[e]pyrano[3,2-b][1,4]oxathiepin-6-one 11-oxide (5a)

Following the general procedure of cyclization by mixing **3a** (50 mg, 0.1mmol) with (0.1 mmol) of NaOMe in a small ballon (50 ml.) under argon at RT for 2 h. The residue was filtered through celite with methanol for 1 min, the solvent then evaporated by rotavap at (25 °C) for (1-2 h.) without purification by flash column chromatography affording the desired product **5a** (34 mg, 0.1 mmol, 98%) as a white amorphous; TLC: R_f = 0.09 (DCM: MeOH 85: 15); **IR** (thin film, neat) ν_{max}/cm^{-1}: 2958, 2923, 2852, 1575, 1540, 1467, 1401, 1378, 1260, 1024, 989; **^{1}H NMR** (300 MHz, $MeOD_4$) δ (ppm): 7.74 – 7.68 (m, 1H), 7.53 – 7.48 (m, 1H), 7.27 (dd, *J* = 5.6, 3.4 Hz, 2H), 4.55 (d, *J* = 9.4 Hz, 1H), 3.93 – 3.87 (m, 1H), 3.75 (dd, *J* = 11.4, 4.8 Hz, 1H), 3.60 (s, 2H), 3.56 – 3.46 (m, 2H); **^{13}C NMR** (75 MHz, $MeOD_4$) δ (ppm): 167.80(C=O), 136.91(C), 126.21(C), 119.71(CH), 119.64(C), 119.26(CH), 118.82(CH), 79.08(CH), 72.66(CH), 69.49(CH), 63.65(CH), 62.01(CH), 53.55(CH_2); **HR-MS(ES +)** *m/z*: for $C_{13}H_{14}NaO_7S$ (M - H^+): m/z calcd 315.0538, found 315.0533.

(2R,3S,4R,4aR,11S,11aS)-5-acetyl-3,4-dihydroxy-2-(hydroxymethyl)-3,4,4a,5-tetrahydro-2H-benzo[f]pyrano[2,3-b][1,4]thiazepin-6(11aH)-one 11-oxide (5b).

Following the general procedure of cyclization by mixing of (50 mg, 0.1 mmol) of **3l** with (70 mg, 0.5 mmol) of K_2CO_3 in a small ballon (50 ml.) under argon at RT for 7 days, the residue was filtered through celite with methanol for 1 min, the solvent then evaporated by rotavap at (25 °C) for (1-2 h.) affording the desired product **5b** (31 mg, 0.099 mmol, 99%) as a yellow solid; **mp** (90-92°C); TLC: R_f = 0.0 (DCM: MeOH 85:15); **IR** (thin film, neat) ν_{max}/cm^{-1}: 2987, , 2923, 1650, 1621, 1557, 1543, 1454, 1400, 1374, 1304, 1169, 1098, 1071, 880, 836, 749, 670, 652; **^{1}H NMR** (400 MHz, $DMSO_{4}$-d_6) δ (ppm):7.56 – 7.48 (m, 2H), 7.26 (td, *J* = 7.7, 1.6 Hz, 1H), 7.15 (td, *J* = 7.5, 1.0 Hz, 1H), 4.80 (d, *J* = 10.5 Hz, 1H), 3.90 – 3.70 (m, 3H), 3.42 (ddd, *J* = 25.3, 17.3, 5.5 Hz, 3H), 1.96 (s, 3H); **^{13}C NMR** (101 MHz, $DMSO_{4}$-d_6) δ (ppm): 174.0 (C=O), 170.4 (C=O), 142.52 (C), 134.5 (C), 130.2 (2CH), 129.5 (CH), 127.05 (CH), 87.60 (CH), 82.0(CH), 77.5 (CH), 72.0 (CH), 62.0 (CH_2), 56.0 (CH), 23.0 (CH_3); HR-MS (APCI negative) m/z: for $C_{15}H_{17}NO_7S$ (M -H^+): m/z calcd 356.0804, found 356.0796.

(2R,3S,4R,11R)-5-acetyl-3,4-dihydroxy-2-(hydroxymethyl)-3,4,4a,5-tetrahydro-2H-benzo[f]pyrano[2,3-b][1,4]thiazepin-6(11aH)-one 11-oxide (5c).

Following the general procedure of cyclization by mixing (50 mg, 0.1 mmol)of **3m** with (27.5 mg, 0.2mmol) of K_2CO_3 in a small ballon (50 ml.) under argon at RT for 2 days., the residue was filtered through celite with methanol for 1 min, the solvent then evaporated under vacuum at (25 °C) for (1-2 h.) then purification by flash column chromatography affording the desired product (34 mg , 0.098 mmol, 98%) as a dark yellow solid; **mp** (244-245°C); TLC: R_f = 0.0(DCM: MeOH 8:2); **IR** (thin film, neat) ν_{max}/cm^{-1}: 1665, 1636, 1576, 1554, 1475, 1455, 1372, 1321, 1098, 1072, 1053, 977, 891, 851, 822, 751, 709, 625; **^{1}H NMR** (300 MHz, $MeOD_4$) δ (ppm): 7.49 (dd, *J* = 7.7, 1.2 Hz, 1H, H_{arom}), 7.34 (dd, *J* = 7.3, 1.8 Hz, 1H, H_{arom}), 7.20 – 7.05 (m, 2H, H_{arom}), 5.52 (d, *J* = 5.1 Hz, 1H, $H_{1',anom}$), 4.02 (dd, *J* = 11.0, 5.1 Hz, 1H, $H_{2'}$), 3.92 (dd, J = 9.8, 4.3 Hz, 1H, $H_{5'}$), 3.72 – 3.60 (m, 3H, $H_{4',6'}$), 3.35 (dd, *J* = 20.6, 11.7 Hz, 1H, $H_{3'}$), 1.81 (s, 3H, NHAc); **^{13}C NMR** (101 MHz, $MeOD_4$) δ (ppm): 173.9 (C=O, C_{lactam}), 161.2 (C=O, NAc), 144.9 (C, C_{lVarom}), 133.0 (C, C_{lVarom}), 132.6 (CH, C_{arom}), 129.7 (CH, C_{arom}), 128.4 (CH), 127.7 (CH_{arom}), 88.8 (CH, $C_{1'anom}$), 75.7 (CH, $C_{5'}$), 72.8 (CH, $_{3'}$), 72.3 (CH, $C_{4'}$), 62.4 (CH_2, $C_{6'}$), 56.3 (CH, $C_{2'}$), 22.7 (CH_3, NHAc); **HR-MS(ESI positive)** *m/z*: for $C_{15}H_{17}NO_6S$ (M+H)$^+$: m/z calcd 356,0804, found 356.0800.

methyl 2-(((2S,3R,4R,5S,6R)-3-acetamido-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)thio)-5-methylbenzoate (6a).

Following the general procedure of coupling, a mixture of (2R,3S,4R,5R,6S)-5-acetamido-2-(acetoxymethyl)-6-((2-(methoxycarbonyl)-4-methylphenyl)thio)tetrahydro-2H-pyran-3,4-diyl diacetate **3b** (50 mg, 0.1 mmol) and with (13.5 mg, 0.1 mmol) of K_2CO_3 in a small ballon (50 ml.) under argon at (50 °C) for 36 h. The residue was filtered through celite with methanol for 1 min, the solvent then evaporated by rotavap at (25 °C) for (1-2 h) then purification by flash column chromatography affording the product **6n** (22 mg, 0.06 mmol, 60%) as a white solid; **mp** (240-241°C); TLC: Rf = 0.67(DCM: MeOH 8: 2); IR (thin film, neat) ν_{max}/cm^{-1}: 2921, 2841, 1630, 1441, 1322, 1301, 1248, 1211, 1072, 1053, 980, 902, 854, 823, 784, 671; **^{1}H NMR** (400 MHz, $DMSO_4$) δ (ppm): δ 7.83 (d, *J* = 8.8 Hz, 1H), 7.62 (d, *J* = 1.4 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.34 (dd, *J* = 8.0,

2.1 Hz, 1H), 4.77 (d, *J* = 10.4 Hz, 1H), 3.80 (s, 3H), 3.71 – 3.57 (m, 2H), 3.17 (s, 3H), 2.30 (s, 3H), 1.78 (s, 3H); **HR-MS(ESI)**: for $C_{17}H_{23}NO_7S$ (M + Na) *m/z* calcd 408.1093, found 408.1096.

Computational methods

Conformations of reactants, products and transition states were fully optimized without constraint using DFT[10e] method with the hybrid Becke-3-parameter-Lee–Yang–Parr exchange-correlation functional and the 6-31G* base as implemented in the Gaussian 09 software package [14].

Vibrational analysis within the harmonic approximation was performed at the same level of theory upon geometrical optimization convergence. Thermodynamic quantities at 298.15 K were calculated using the zero-point and thermal energy corrections derived from unscaled frequencies. Local minima and first-order saddle points were characterized by their respective numbers of imaginary frequencies. Minimum energy path were followed as defined by the intrinsic reaction coordinate[15]. Figures were rendered with GaussView[16].

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