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Stereoselective synthesis of new glycooxathiecinone using *vic*-cyclic thionocarbonate haloalkylation and ring closing metathesis as key steps

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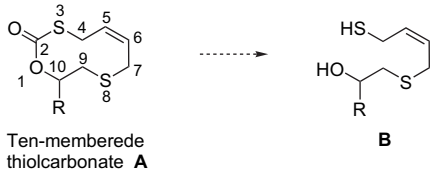
ABSTRACT

Herein, we describe the first glycoconjugate macrocyclic thiolcarbonate namely (*Z*)-10(*S*)-[3′-*O*-acetyl-1′,2′-*O*-isopropylidene-4′-deoxy-D-erythrofuranose]-4,7,9-trihydro-10*H*-8-thia-1,3-oxathiecin-2-one (**17a**) using a strategy based on two key steps synthesis: (i) a haloalkylation of *vic*-diol via their cyclic thionocarbonate derivatives; (ii) a macrocyclisation using ring closing metathesis reaction. Detailed here is a newly developed extension of *vic*-diol halogenation via the cyclic thionocarbonate function but using a range of alkyl halides other than the customarily used MeI. For example, with 1,2-*O*-isopropylidene-5,6-*O*-thionocarbonate-D-glucose (**1**) and allyl bromide, the 5-allylthiolcarbonate-6-bromo-6-deoxy-D-glucose derivative **6** was obtained in good yield. The later submitted to 6-allythioetherification and ring closing metathesis (RCM) with Grubbs second generation gave stereoselectively the target oxathiecinone **17a** in 75% yield for the RCM step.

1. Introduction

The 1,3-oxathiecin[1a] prototype **A** belonging to 10-membered macrocyclic thiolcarbonate family[1b–f] in which the C-8 carbon atom was replaced by sulfur atom and where the C-10 carried sugar moiety (Scheme 1) has recently attracted our interest for three reasons: firstly this type of 10-membered macrocyclic skeleton and the glycoconjugate analogues thereof are scarce; secondly, stereocontrolled formation of a carbon–carbon double bond often a critical step in a synthetic strategies; and lastly, the relative lack of investigations into these compounds as therapeutic leads. Amongst such biological effects that should be mentioned is their antioxidant effect. In fact, simultaneous presence of two sulfur atoms in allylic positions has the potential to confer interesting antioxidant properties by analogy to various thiolallyl ethers that have been extracted from Liliaceae plants (e.g., garlic, onion…) (Fig. 1).[2] The later antioxidant effect was recently ascribed to allylsulfinic acid species generated from Cope elimination of corresponding allylsulfoxide (Fig. 2).[3] An alternative mechanism described for hydroxylated allylselenaether argues that allyl group is involved in a free radical scavenging effect via 1,3-sigmatropic rearrangement of the corresponding selenoxide to selininate ester intermediate (Fig. 2).[4] It should be pointed out that the cleavage of these type of thiolcarbonate could lead to allylic thiol **B**, which in principle could have much potential in terms of further chemical transformations and also biologic applications.



Scheme 1.

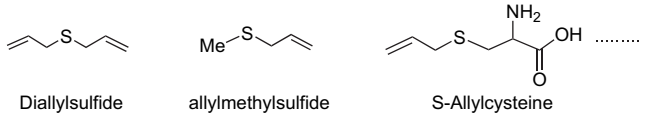


Figure 1. Some thiol lalyl ether with cancer chemioprotect ion effect from Liliaceaes plants.

Figure 2.

1,3-Oxathiecin-2-ones have been already reported by Kurihara and co-workers.[1] However, these carried no more than one sulfur atom and were devoid of any sugar moiety. Their synthetic strategy

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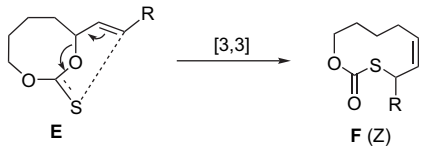
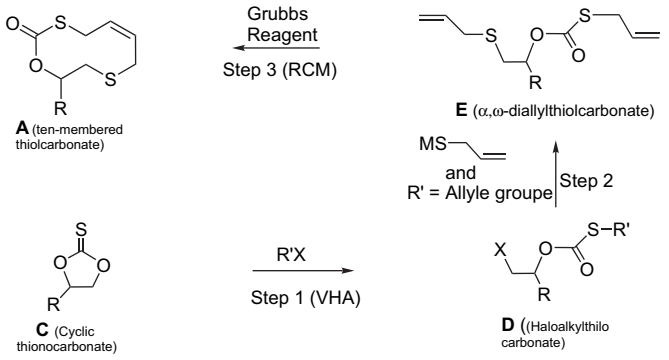
used involved a [3,3]-sigmatropic rearrangement of allylic cyclic thionocarbonate as key step (Scheme 2).



Scheme 2. Exemple of (*Z*)-10-membered macrocyle from sygmatropic cyclic thionocarbonate **1**.

We considered an alternative strategy for obtaining the first example of a glycoconjugate macrocyclic (*Z*)-1,3-oxathiecin-2-one **A**. The synthesis involves three key steps (Scheme 3): the first is an extension of the well known *vic*-diol cyclic thionocarbonate haloalkylation (VHA) of **C** intermediate (R=sugar) to the newly haloallyl thiolcarbonate **D** (R′=allyle). To the best of our knowledge, only Vedejs and Wu in 1974[5] have reported alternatives to the classical MeI used in this reaction and showed that when *i*-PrI was used instead,[6] *vic*-cyclic thionocarbonates underwent β-elimination which competes with the desired VHA reaction. Thus we chose to investigate the behaviour of a range of additional alkyl halides with thionocarbonate precursors. The second and third steps are, respectively, the thiollayletherification to α,ω-dienne **E** and ring closing metathesis (RCM) to **A**.



Scheme 3. Three steps synthesis of 10-membered thiolcarbonate from cyclic thionocarbonate.

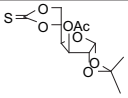
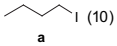
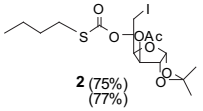
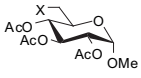
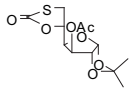
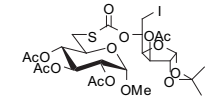
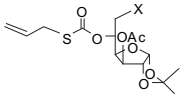
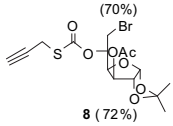
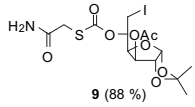
The primary challenge of this strategy would be to overcome any possible unfavourable effect of the sulphide functions in the RCM precursor on the subsequent coupling reaction.[7] Such an effect has been described in the literature and attributed to catalyst inactivation of the metal by S-coordination. The second challenge would be to avoid possible ring-opening metathesis polymerisation due to the ring strain generated upon macrocyclisation.[8]

2. Results and discussion

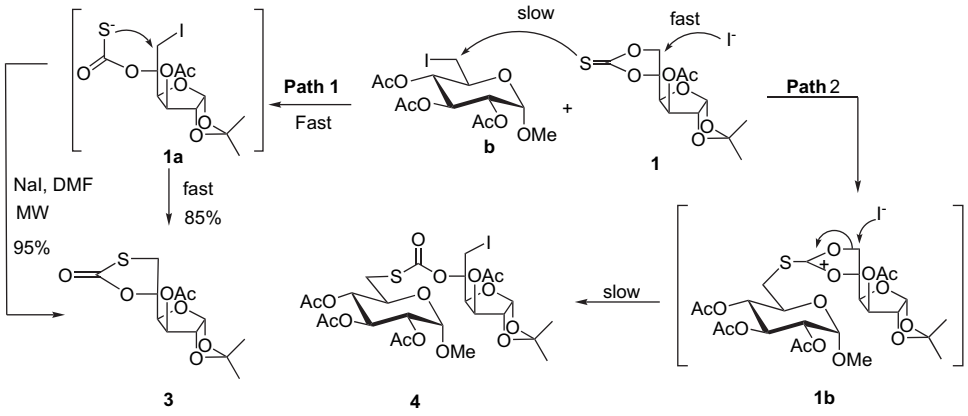
3-*O*-Acetyl-1,2-isopropylidene-5,6-thionocarbonyl-D-glucofuranose (**1**)[9] when treated with large excess of *n*-BuI (10 equiv) under solvent-free conditions at 50 °C in a closed reactor (conditions used in previous work with MeI as halogenating reagent),[10] no reaction occurred even after prolonged times. In contrast, increasing the temperature to 130 °C (Table 1, entry 1) gave after 16 h, the 6-iodo-5-*n*-butylthiolcarbonate derivative **2** in 75% yield. The reaction time could be reduced to 30 min under solvent-free microwaves (μW) conditions in CEM-Descover apparatus to give **2** with similar yield (77%). Two carbonyl signals at 169.5/170.6 ppm, and C-6 carbon atom at 6.5 ppm were characteristic of compound **2**.

We were then interested in using the sugar halide derivative **b**[11] possessing a D-*gluco* configuration as haloalkylating reagent in

Table 1
Halogenation of 3-*O*-acetyl-1,2-*O*-isopropylidene-5,6-thionocarbonyl-D-glucofuranose under thermal or μW conditions

Entry	Cyclic thiono carbonate	RX (equiv)	Thermal heat (Δ) *t*(°C)	W (watts)**	time	solvent		Product (yield)^{W} (yield)$^{\Delta}$
1	 **1** D-*Gluco*	 (10) **a**	130	Δ	16 h	free		 **2** (75%) (77%)
			130	300	30 min	"		
2	"						 +	
		b X = I (2)	130	Δ	3 h	DMF	**3** (80%)	**4***
			130	300	30 min	DMF	(85%)	"
		b' X = Cl (2)	160	300	30 min	DMF	(80%)	"
3	"							
		c X = Cl (10)	120	Δ	6 d	free		**5** : X = Cl (32 %)
			120	250	20 min	"		(40 %)
		d X = Br (10)	120	Δ	3 h	free		**6** : X = Br (90%)
			120	250	20 min	"		(82%)
		e X = I (10)	120	Δ	1 h	free		**7** : X = I (62%)
			85	250	10 min	"		(70%)
4	"	 (10) **f**	120	Δ	3 h	free		 **8** (72%)
			120	250	20 min	"		
5	"	 (5)						
		g	100	Δ	30 min	DMF		**9** (88 %)

W = μW conditions; Δ = Thermal heating; *Detected by MS-electrospray; ** Initial power.



Scheme 4. The cyclic thionocarbonate-thiolcarbonate isomerisation with halosugars as alkyl halide.

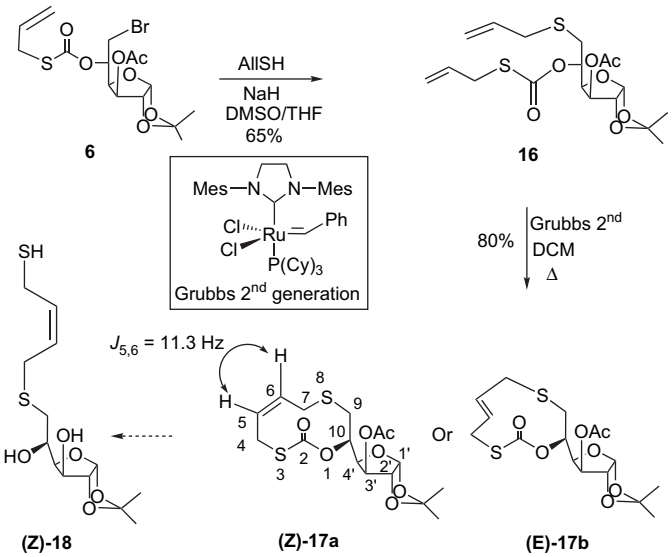
order to obtain the thiolcarbonate bridged disaccharidic compound **4** (Entry 2). Although trace amounts of the later compounds were indeed detected by electrospray mass spectroscopy, the thiolcarbonate derivative **3**[9] issuing from the Schönberg rearrangement was obtained as the major product (85%) under both conventional heating and μW conditions. Compound **3** is easily characterised by the presence of C-6 signal at 32.8 ppm instead of that for the cyclic thionocarbonate **1**, which appears at 70 ppm. The catalytic amount of I^- formed in situ probably accounts for the observed isomerisation following the mechanism described in path 1 of the Scheme 4.

The desired reaction (path 2, Scheme 4) is likely to be slow due to the steric hindrance of the saccharidic moiety and/or the **b**/**1** ratio (only 2/1). The involvement of I^- ion was confirmed by reacting **1** with a catalytic amount of NaI, which led to the rearrangement product **3** in excellent yield (85%). Although the catalytic effect of the I^- ion on the Schönberg isomerisation under thermal conditions has already been reported,[12] this is the first example where it occurs efficiently and in a short time under μW conditions. To avoid this catalytic isomerisation we explored the reaction using 6-chloro-α-D-glucopyranoside derivative **b′**,[11] which could generate Cl^-, which is far less nucleophil than I^- (Entry 2). However the same results under μW conditions but at 160 °C reaction temperature for completion. This transformation is currently under further investigation.

In an attempt to facilitate a reaction proceeding via the desired S_N2 mechanism and thus to obtain the key metathesis precursor required for macrocyclisation formation, we explored the VHA reaction of **1** with allyl halides **c**, **d**, and **e**, respectively (Entry 3). The reaction of allyl chloride **c** is very slow (6 days) under conventional conditions (at 120 °C). The 6-chloro-5-allylthiolcarbonate derivative **5** was obtained in only moderate yield (32%). A similar yield of **5** was obtained under μW and solvent-free conditions, but a greatly reduced reaction time (30 min) at 120 °C. Use of allyl bromide **d** as alkylating reagent gave the bromothiolcarboante **6** in yield of up to 82% under μW conditions at 120 °C, whereas with allyl iodide **e** the 6-iodo analogue **7** was obtained in much milder conditions (85 °C and 10 min). All compounds **5**, **6** and **7** were characterised by NMR spectroscopy and especially signals at 44.6, 32.9 and 6.4 ppm corresponding to their halogenated C-6 carbon atoms, respectively.

To further improve the generality of this one-pot haloalkylation, two further alkyl halides namely propargyl bromide (**f**) and acetamide iodide (**g**), were allowed to react with **1**. Only 20 min were needed to efficiently give **8** (72%) with **f** (10 equiv) under μW solvent-free conditions (Entry 4) and with activated alkyl halide reagent **g** (Entry 5), the reaction gave the 5-acetamido-6-iodo-thiolcarbonate **9** in excellent yield (88%) under conventional thermal conditions (120 °C) in reaction time of only 30 min.

Although, the VHA reaction is well known, its generalisation to the use of a range of alkyl halide (≠ MeI) such as allyl bromide is of great interest not least because it allows the subsequent synthesis of macrocyclic thiolcarbonate **17** (Scheme 5). In fact, as shown previously, the VHA reaction leads to the compound **6** with D-*gluco* configuration in excellent yield (90%) (Entry 3). This key intermediate was subsequently thioetherified with allylthiol to lead to α,ω-diene **16** in 65% yield. The later when submitted to RCM reaction with Grubbs second generation as catalyst, it gave stereoselective access to one 10-membered thiolcarbonate isomer **17a** or **17b** in good yield (75%).



Scheme 5.

In the absence of single crystal X-ray data the olefin configuration in **17** was not established by RX spectroscopy. In ^1H NMR spectroscopy 10-membered ring with *Z*-configuration usually displays ^3J-coupling constants in range of between 10.5 and 11.8 Hz. This is the case for the hetero-macrocyclic compounds **E** obtained from an RCM reaction,[13] or **F** and **G** obtained from [3,3]-sigmatropic rearrangement of adjacent allyl cyclic thionocarbonate[1b–f] (Fig. 3). The thiolcarbonate **H** with *E*-configuration is characterised by larger coupling constants (15.3 Hz).[1e] We therefore conclude by analogy that compound **17** with a ^3J-coupling constant equal to 11.3 Hz, is in its *Z*-configuration form **17a**.

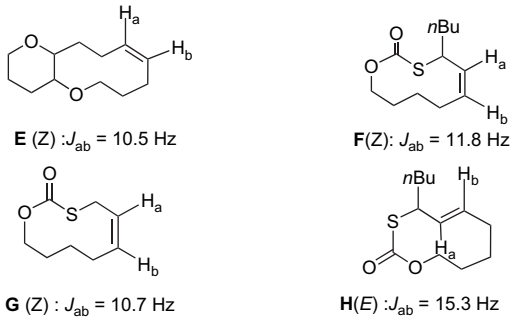


Figure 3. Example of *Z*-10-membered macrocyles with corresponding ^3J coupling constant.

It should be emphasised that in contrast to previously described thiolcarbonate such as **F** and **G**, **17a** features a sugar moiety and more than one sulfide atom. After alkaline methanolysis, **17a** should lead to the corresponding thiol (*Z*)-**18**.

3. Conclusion

The ring closing metathesis has been successfully used in short and stereoselective synthesis of unpublished glycoconjugate 10-membered macrocyclic thiolcarbonate namely (*Z*)-10(*S*)-[3′-*O*-acetyl-1′,2′-*O*-isopropylidene-4′-deoxy-D-erythrofuranose]-4,7,9-trihydro-10*H*-8-thia-1,3-oxathiecin-2-one (**17a**). The α,ω-diene thiolcarbonate backbone was obtained from the first extension of *vic*-diol haloalkylation via the cyclic thionocarbonate function as key step. Further developments of this attractive strategy are in our ongoing research program.

4. Experimental

4.1. General methods

Syntheses under microwave irradiation were performed under pressure conditions with single-mode CEM-Discover apparatus (2450 MHz) in conditions reported in Table 1. All chemical reagents were purchased from Aldrich or Acros (France). Melting points were determined with a Buchi 535 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker 300 WB spectrometer; chemical shifts are reported in δ (ppm). All ^{13}C NMR signals were assigned through C, H-correlated spectra with hsqc.grad experiment. TLC was performed on silica Gel 60 F_{254} 230 mesh (E. Merck) with cyclohexane/EtOAc as eluent, and spots were detected by vanillin/H_2SO_4 reagent. Preparative column chromatography was performed using 230–400 mesh Merck silica gel (purchased from Aldrich). Optical rotations were determined with Perkin Elmer instruments, model 343 polarimeter (1 ml cell). Low resolution electrospray mass spectra (ESI-MS) in the positive ion mode were obtained on Waters-Micromass ZQ quadripole instrument equipped with an electrospray (Z-spray) ion source (Waters-Micromass, Manchester, U.K.). High resolution electrospray experiments (ESI-HRMS) were performed on a Waters-Micromass Q-TOF *Ultima Global* hybrid quadrupole time-of-flight instrument, equipped with an electrospray (Z-spray) ion source (Waters-Micromass, Manchester, U.K.).

4.2. General procedure for the preparation of halogenoalkylthiolcarbonate

4.2.1. Method A. Microwave conditions. The mixture of substrate and alkyl halide was reacted under pressure and stirred in pressurised 'vial' purchased from CEM-Corporation, under free solvent conditions unless mentioned. Time and temperature are reported in Table 1. In all μW experiments, TLC was performed every 10 min and the reaction stopped after complete disappearance of starting material. The power and temperature max were fixed under pressure control system. Volatiles removed under pressure and the crude product obtained was purified by chromatography on silica gel with cyclohexane/EtOAc mixture as eluent.

4.2.2. Method B. Thermal heating conditions. The substrate and alkyl halide were reacted under pressure and stirred in a closed reactor at temperatures indicated in Table 1. The crude product obtained after concentration was purified by chromatography on silica gel with cyclohexane/EtOAc mixture as eluent.

*4.2.3. 3-O-Acetyl-5-O-n-butylthiocarbonyl-6-iodo-6-deoxy-1,2-O-isopropylidene-α-D-glucofuranose (**2**).*

4.2.3.1. Method A. 3-*O*-Acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**1**)[6] (100 mg, 0.33 mmol) and 1-iodobutane (0.38 ml, 3.3 mmol) were reacted under 250 W microwave irradiation, at 120 °C during 30 min. Compound **2** was isolated as a yellow syrup (120 mg, 75%) after flash chromatography with (5:1, cyclohexane/EtOAc) mixture as eluent.

4.2.3.2. Method B. 1-Iodobutane (0.38 ml, 3.3 mmol) and **1** (100 mg, 0.33 mmol) were reacted at 120 °C in a closed reactor overnight to give the desired product **2** in a 72% yield. $[\alpha]_D^{20}$ −28 (*c* 0.1, $CHCl_3$); R_f=0.3 (9:1, cyclohexane/EtOAc). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=170.6, 169.5 (C=O), 112.9 (*C*(*i*-Pr)), 105.1 (C-1), 83.4 (C-2), 79.6 (C-5), 74.8 (C-4), 70.4 (C-3), 31.7 (C-2′), 30.9 (C-1′), 27.0 (*C*H$_3$(*i*-Pr)), 26.5 (*C*H$_3$(*i*-Pr)), 21.8 (C-3′), 20.8 (CH$_3$),13.6 (C-4′), 6.5 (C-6). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=5.90 (d, *J*=3.6 Hz, 1H; H-1), 5.27 (d, *J*=3.0 Hz, 1H; H-4), 4.90–5.00 (m, 1H; H-3), 4.50 (d, *J*=3.5 Hz, 1H; H-2), 4.30 (dd, *J*=3.0 Hz, 1H; H-5), 3.60 (dd, *J*=3.0 and 11.3 Hz, 1H; H-6a), 3.30 (dd, *J*=5.6 and 11.3 Hz, 1H; H-6b), 2.85 (ddd, *J*=3.3 and 3.5 Hz, 2H; H-1′), 2.10 (s, 3H; C(O)*C*H$_3$), 1.70–1.60 (m, 2H; H-2′), 1.58 (s, 3H; *C*H$_3$(*i*-Pr)), 1.50–1.40 (m, 2H; H-3′), 1.3 (s, 3H; *C*H$_3$(*i*-Pr)), 0.9 (t, *J*=7.32 Hz, 3H; H-4′). HRMS calcd for $C_{16}H_{25}IO_7SNa$ [(M^+Na)$^+$] 511.0263; found 511.0283.

*4.2.4. 3-O-Acetyl-5-O-allylthiocarbonyl-6-chloro-6-deoxy-1,2-O-isopropylidene-α-D-glucofuranose (**5**).*

4.2.4.1. Method A. Allyl chloride (0.27 ml, 3.3 mmol) and **1** (100 mg, 0.33 mmol) were reacted under 250 W microwave irradiation, at 120 °C during 30 min. After concentration and flash chromatography (5:1, cyclohexane/EtOAc), **5** was isolated as a yellow syrup (100 mg, 40%).

4.2.4.2. Method B. Allyl chloride (0.27 ml, 3.3 mmol) and **1** (100 mg, 0.33 mmol) were reacted at 120 °C in a closed reactor for 6 days to give **5** in a 32% yield. $[\alpha]_D^{20}$=−9 (*c* 0.1, $CHCl_3$); R_f=0.3 (5:1, cyclohexane/EtOAc); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=170.0, 169.5 (each C=O), 132.6 (C-2′), 118.6 (C-3′), 112.9 (*C*(*i*-Pr)), 105.2 (C-1), 83.3 (C-2), 76.9 (C-5), 75.0 (C-4), 71.5 (C-3), 44.7 (C-6), 34.0 (C-1′), 26.9, 26.4 (*C*H$_3$(*i*-Pr)), 20.8 (*C*H$_3$CO). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=5.90 (d, *J*=3.6 Hz, 1H; H-1), 5.88–5.75 (m, 2H; H-2′), 5.42–5.08 (m, 4H; H-3, H-4 and H-3′), 4.50 (d, *J*=3.7 Hz, 1H; H-2), 4.46 (dd, *J*=2.9 Hz, 1H; H-5), 3.90 (dd, *J*=2.6 and 12.4 Hz, 1H; H-6a), 3.75 (dd, *J*=5.5 and 12.4 Hz, 1H; H-6b), 3.50–3.40 (m, 2H; H-1′), 2.04 (s, 3H; *C*H$_3$CO), 1.50 (s, 3H; *C*H$_3$(*i*-Pr)), 1.25 (s, 3H; *C*H$_3$(*i*-Pr)). HRMS calcd for $C_{15}H_{21}ClNaO_7S$ [(M^+Na)$^+$] 403.0594; found 403.0590.

*4.2.5. 3-O-Acetyl-5-O-allylthiocarbonyl-6-bromo-6-deoxy-1,2-O-isopropylidene-α-D-glucofuranose (**6**).*

4.2.5.1. Method A. Allyl bromide (0.28 ml, 3.3 mmol) and **1** (100 mg, 0.33 mmol) were reacted under 250 W microwave irradiation, at 120 °C during 30 min. After concentration and flash chromatography (5:1, cyclohexane/EtOAc), **6** was isolated as a yellow syrup (125 mg, 90%).

4.2.5.2. Method B. Allyl bromide (0.28 ml, 3.3 mmol) and **1** (100 mg, 0.33 mmol) were reacted at 120 °C in a closed reactor for 3 h to give 6 with an 82% yield. $[\alpha]_D^{20}=-30$ (*c* 0.1, $CHCl_3$); R_f=0.3 (5:1, cyclohexane/EtOAc); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=169.9, 169.4 (C=O), 132.6 (C-2′), 118.5 (C-3′), 112.9 (*C*(*i*-Pr)), 105.2 (C-1), 83.3 (C-2), 77.9 (C-5), 74.9 (C-4), 70.9 (C-3), 34.0 (C-1′), 32.9 (C-6), 26.9, 26.4 (*C*H_3 (*i*-Pr)), 20.8 (*C*H_3CO); ^1H NMR ($CDCl_3$, 300 MHz): δ=5.88 (d, *J*=3.7 Hz, 1H; H-1), 5.88–5.75 (m, 2H; H-2′), 5.35–5.10 (m, 4H; H-3, H-4 and H-3′), 4.48 (d, *J*=3.5 Hz, 1H; H-2), 4.42 (dd, *J*=3.0 Hz, 1H; H-5), 3.75 (dd, *J*=2.7 and 11.6 Hz, 1H; H-6a), 3.58 (dd, *J*=5.6 and 11.6 Hz, 1H; H-6b), 3.50–3.47 (m, 2H; H-1′), 2.04 (s, 3H; *C*H_3CO), 1.50 (s, 3H; *C*H_3(*i*-Pr)), 1.26 (s, 3H; *C*H_3 (*i*-Pr)). HRMS calcd for $C_{15}H_{21}BrNaO_7S$ [$(M^+Na)^+$] calcd 447.0089; found 447.0074.

*4.2.6. 3-O-Acetyl-5-O-allylthiocarbonyl-6-iodo-6-deoxy-1,2-O-isopropylidene-α-D-glucofuranose (**7**).*

4.2.6.1. Method A. Allyl iodide (0.30 ml, 3.3 mmol) and **1** (100 mg, 0.33 mmol) were reacted under 250 W microwave irradiation, at 120 °C during 10 min. After concentration and flash chromatography (5:1, cyclohexane/EtOAc), **7** was isolated as a yellow syrup (96 mg, 70%).

4.2.6.2. Method B. Allyl iodide (0.75 ml, 8.3 mmol) and **1** (250 mg, 0.83 mmol) were reacted in a closed reactor at 120 °C for 1 h to give **7** with a 62% yield. $[\alpha]_D^{20}=-19$ (*c* 0.1, $CHCl_3$); R_f=0.3 (6:1, cyclohexane/EtOAc); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=169.7, 169.4 (C=O), 132.6 (C-2′), 118.5 (C-3′), 112.8 (*C*(*i*-Pr)), 105.1 (C-1), 83.3 (C-2), 79.5 (C-5), 74.7 (C-4), 70.6 (C-3), 34.0 (C-1′), 26.9, 26.4 (*C*H_3 (*i*-Pr)), 20.8 (*C*H_3CO), 6.4 (C-6). ^1H NMR ($CDCl_3$, 300 MHz): δ=5.84 (d, *J*=3.7 Hz, 1H; H-1), 5.83–5.75 (m, 2H; H-2′), 5.30–5.10 (m, 2H; H-4 and H-3′), 4.93–4.86 (m, 1H; H-3), 4.46 (d, *J*=3.6 Hz, 1H; H-2), 4.30 (dd, *J*=3.0, 1H; H-5), 3.58 (dd, *J*=3.1 and 11.4 Hz, 1H; H-6a), 3.45–3.40 (m, 2H; H-1′), 3.38 (dd, *J*=5.6 and 11.4 Hz, 1H; H-6b), 2.00 (s, 3H; *C*H_3CO), 1.50 (s, 3H; *C*H_3(*i*-Pr)), 1.26 (s, 3H; *C*H_3(*i*-Pr)). HRMS for $C_{15}H_{21}INaO_7S$ [$(M^+Na)^+$] calcd 494.9951; found 494.9955.

*4.2.7. 3-O-Acetyl-6-bromo-6-deoxy-5-O-propargylthio-carbonyl-1,2-O-isopropylidene-α-D-glucofuranose (**8**).*

4.2.7.1. Method A. Propargyl bromide (0.71 ml, 6.6 mmol) and **1** (200 mg, 0.67 mmol) were reacted under 250 W microwave irradiation, at 120 °C during 30 min. After concentration and flash chromatography (5:1, cyclohexane/EtOAc), **8** was isolated as a yellow syrup (195 mg, 70%).

4.2.7.2. Method B. Propargyl bromide (0.71 ml, 6.6 mmol) and **1** (200 mg, 0.67 mmol) were reacted at 120 °C in a closed for 3 h to give the desired product **8** with a 72% yield. $[\alpha]_D^{20}=-23$ (*c* 0.1, $CHCl_3$); R_f=0.3 (5:1, cyclohexane/EtOAc); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=170.0, 169.5 (C=O), 112.9 (*C*(*i*-Pr)), 105.2 (C-1), 83.3 (C-2), 78.2 (C-2′), 77.8 (C-5), 74.9 (C-4), 71.9 (C-3′), 71.6 (C-3), 32.7 (C-1′), 26.9, 26.4 (*C*H_3(*i*-Pr)), 20.8 (*C*H_3CO), 19.8 (C-6). ^1H NMR ($CDCl_3$, 300 MHz): δ=5.90 (d, *J*=3.5 Hz, 1H; H-1), 5.40–5.30 (m, 1H; H-3), 5.25 (d, *J*=2.7 Hz, 1H; H-4), 4.50 (d, *J*=3.6 Hz, 1H; H-2), 4.60 (dd, *J*=3 Hz, 1H; H-5), 3.68 (dd, *J*=2.7 and 11.7 Hz, 1H; H-6a), 3.53 (dd, *J*=5.5 and 10.1 Hz, 1H; H-6b), 3.60 (d, *J*=5.5 Hz, H-1′), 2.25 (t, *J*=2.7 Hz, 1H; H-3′), 2.10 (s, 3H; C(O)CH_3), 1.50 (s, 3H; *C*H_3(*i*-Pr)), 1.26 (s, 3H; *C*H_3(*i*-Pr)). HRMS calcd for $C_{15}H_{19}BrNaO_7S$ [$(M^+Na)^+$] 446.9913; found 446.9913.

*4.2.8. 5-O-Acetamidothiocarbonyl-3-O-acetyl-6-iodo-6-deoxy-1,2-O-isopropylidene-α-D-glucofuranose (**9**).*

4.2.8.1. Method B. The mixture of iodoacetamide (310 mg, 1.65 mmol) and **1** (100 mg, 0.33 mmol) in dried toluene (0.5 ml) was reacted at 120 °C in a closed reactor for 1 h. After concentration and flash chromatography (1:1, cyclohexane/EtOAc), **9** was isolated as a yellow syrup (142 mg, 88%). $[\alpha]_D^{20}=-19$ (*c* 0.1, $CHCl_3$); R_f=0.3 (1:1, cyclohexane/EtOAc); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=170.6, 170.1, 169.6 (C=O), 113.1 (*C*(*i*-Pr)), 105.1 (C-1), 83.4 (C-2), 79.6 (C-5), 74.5 (C-4), 71.6 (C-3), 34.1 (C-1′), 27.0, 26.4 (*C*H_3 (*i*-Pr)), 20.9 (*C*H_3CO), 5.7 (C-6).^1H NMR ($CDCl_3$, 300 MHz): δ=6.70–6.30 (br d, 2H; NH_2), 5.90 (d, *J*=3.5 Hz, 1H; H-1), 5.35 (d, *J*=3.5 Hz, 1H; H-4), 5.00–4.90 (m, 1H; H-3), 4.50 (d, *J*=3.5 Hz, 1H; H-2), 4.60 (dd, *J*=2.8 and 2.8 Hz, 1H; H-5), 4.00–3.60 (m, 4H; H-6 and H-1′), 2.08 (s, 3H; C(O)CH_3), 1.50 (s, 3H; *C*H_3(*i*-Pr)), 1.30 (s, 3H; *C*H_3(*i*-Pr)). HRMS calcd for $C_{14}H_{20}INaNO_8S$ [$(M^+Na)^+$] 511.9852; found 511.9837.

*4.2.9. 6-S-Allylthioether-5-O-allylthiolcarbonate-1,2-O-isopropylidene-α-D-glucofuranose (**16**).* To a cooled solution of **6** (280 mg, 0.79 mmol) in 1:1 DMSO/THF (4 ml) were added allylthiol (132 μl, 0.95 mmol) and $CsCO_3$ (310 mg, 0.95 mmol). The mixture was stirred for 15 min at 0 °C. After extraction with ether/H_2O, the organic layer was dried on $MgSO_4$ and concentrated. The chromatography on silica gel with 95:5 cyclohexane/EtOAc as eluent, gave compound **16** as syrup in 60% yield (165 mg). $[\alpha]_D^{20}=-22$ (*c* 0.1, $CHCl_3$); R_f=0.32 EtOAc/cyclohexane (5/95; v/v); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=169.9, 169.7 (C=O), 134.0 (C-2′), 132.9 (C-8), 118.5 (C-9), 117.9 (C-3′), 112.7 (*C*(*i*-Pr)), 105.2 (C-1), 83.5 (C-2), 78.5 (C-4), 75.2 (C-3), 71.9 (C-5), 35.4 (C-6), 34.7 (C-1′), 32.6 (C-7), 26.9, 26.4 (*C*H_3 (*i*-Pr)), 20.9 (*C*H_3 (OAc))ppm. ^1H NMR ($CDCl_3$, 300 MHz): δ=5.88 (d, *J*=3.0 Hz, 1H; H-1), 5.85–5.65 (m, 2H; H-2′ and H-8), 5.35–5.10 (m, 6H; H-3, H-4, H-3′ and H-9), 4.50 (d, *J*=3.1 Hz, 1H; H-2), 4.45 (dd, *J*=2.1 and 6.2 Hz, 1H; H-5), 3.51–3.45 (m, 2H; H-1′), 3.15 (d, *J*=7.2 Hz, 2H; H-7), 3.10 (dd, *J*=3.0 and 14.9 Hz, 1H; H-6b), 2.70 (dd, *J*=7.0 and 14.9 Hz, 1H; H-6a), 2.05 (s, 3H, *C*H_3 (OAc)), 1.57 (s, 3H; *C*H_3(*i*-Pr)), 1.3 (s, 3H; *C*H_3 (*i*-Pr)) ppm. HRMS calcd for $C_{18}H_{26}O_7S_2$ [$(M^+Na)^+$] calcd 441.1018; found 441.1016.

*4.2.10. Synthesis of 10-membered thiolcarbonate **17a**: (Z)-10(S)-[3′-O-acetyl-1′,2′-O-isopropylidene-4′-deoxy-D-erythrofuranose]-4,7,9-trihydro-10H-8-thia-1,3-oxathiecin-2-one.* To a solution of **16** (50 mg, 0.12 mmol) in distilled and degazed CH_2Cl_2 (25 ml), was added Grubbs second generation (15 mg, 0.018 mmol, in 1 ml of CH_2Cl_2). The mixture was stirred at 50 °C for 2 h. The compound **17a** was isolated in 75% yield (35 mg) after chromatography on silica gel with 95:5 cyclohexane/EtOAc as eluent. $[\alpha]_D^{20}=-27$ (*c* 0.1, $CHCl_3$); R_f=0.3, 95:5 cylohexane/EtOAc. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=169.9, 168.2 (C=O), 128.3 (C-6), 127.9 (C-5), 113.1 (*C*(*i*-Pr)), 105.2 (C-1′), 83.5 (C-2′), 76.1 (C-4′), 74.6 (C-3′), 72.9 (C-10), 30.7 (C-9), 29.0 (C-4), 28.0 (C-7), 27.2, 26.7 (*C*H_3 (*i*-Pr)), 20.9 (*C*H_3 (OAc)) ppm; ^1H NMR ($CDCl_3$, 300 MHz): δ=5.90 (d, *J*=3.36 Hz, 1H; H-1′), 5.75 (tq, *J*=4.6 and 11.2 Hz, 1H; H-5), 5.67 (dt, *J*=2.7 and 9.6 Hz, 1H; H-10), 5.51 (dt, *J*=3.2 and 11.3 Hz, 1H; H-6), 5.40 (d, *J*=2.5 Hz, 1H; H-3′), 4.95 (dd, *J*=2.7 and 9.6 Hz, 1H; H-4′), 4.50 (d, *J*=3.4 Hz, 1H; H-2′), 4.10 (t, *J*=13.9 Hz, 1H; H-4b), 3.85 (t, *J*=13.5 Hz, 1H; H-7b), 2.96 (dd, *J*=1.8 and 15.5 Hz, 1H; H-9b), 2.87 (d, *J*=14.0 Hz, 1H; H-7a), 2.81 (dd, *J*=4.5 and 13.7 Hz, 1H; H-4a), 2.68 (dd, *J*=3.2 and 15.5 Hz, 1H; H-9a), 2.05 (s, 3H, *C*H_3 (OAc)), 1.60 (s, 3H; *C*H_3(*i*-Pr)), 1.50 (s, 3H; *C*H_3 (*i*-Pr)) ppm. HRMS pour $C_{16}H_{22}O_7S_2$ [$(M^+Na)^+$] calcd 413.0705; found 413.0700.

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