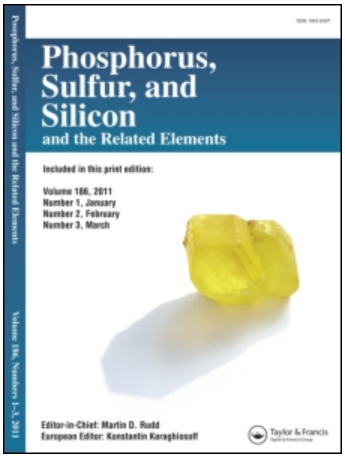

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SYNTHESIS OF DITHIO-, THIO-AND CARBAMOYL ESTER DERIVATIVES OF MONOSACCHARIDES AND ITOLS

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SYNTHESIS OF DITHIO-, THIO- AND CARBAMOYL ESTER DERIVATIVES OF MONOSACCHARIDES AND ITOLS

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Regiospecific carbamoylation of *O*-isopropylidene protected monosaccharides and itols gave a large range of novel carbamoyl, thiocarbamoyl and dithiocarbamoyl esters. These fully, partially and unprotected carbohydrates possess both modulable hydrophilic character and potential biological properties. Some carbamoyl esters showed, by NMR spectroscopy, characteristics of Z-E isomerism; the rotational energy barrier was higher for the thiocarbamates than for the corresponding carbamates.

Keywords: Dithiocarbamate; thiocarbamate; carbamate; carbohydrate; Z-E isomerism; NMR

INTRODUCTION

Carbamates are known to be biologically active and found to have medicinal[1-4] and agricultural[5-10] applications. Their biological properties vary in accordance with the type of carbamoyl group[11] such as when either or both oxygen atoms are replaced by sulphur atoms and when the nitrogen atom has one or two alkyl chains. Moreover literature reported that the association of a carbohydrate moiety with carbamates enhances the polarity,[12] the phloem mobility,[12] and increases plant systemic activity.[13] Thus we have prepared a large range of carbamoyl ester carbohydrate derivatives. D-Glucose, D-galactose, xylitol, and glycerol were chosen for derivatization since they are inexpensive and can readily converted to *O*-isopropylidene protected derivatives with one remaining hydroxyl

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group unprotected. Thus carbamoylation of the carbohydrate intermediates can then be effected regiospecifically at either the unprotected primary or secondary hydroxyl groups. This can be achieve either in one step to form *O*-carbamates and *O*-thiocarbamates or following activation to give *S*-carbamates and *S*-thiocarbamates. In accordance with the number of unprotected hydroxyl groups chosen in the final product, modulation of the hydrophilic-lipophilic balance (HLB) may be effected. This strategy permit to design a wide variety of carbamoyl ester carbohydrate derivatives which can be readily targeted to specific applications.

RESULTS AND DISCUSSION

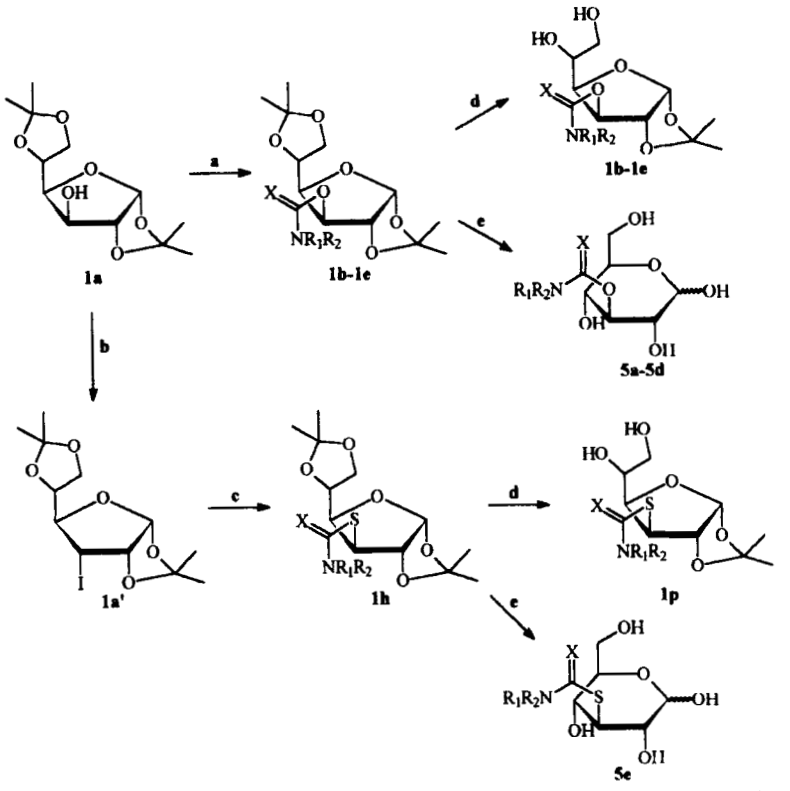
The synthetic steps employed to synthesize the range of carbamoyl esters described in this paper are amplified in Scheme 1 for the D-glucose derivatives. A similar strategy was employed for the synthesis of D-galactose, xylitol, and glycerol. Some *N*-ethylcarbamoyl esters were converted to their *N*-ethyl-*N*-methylcarbamoyl analogues (scheme 2). The hydrophilic character can be increased by selective partial or total deprotection of the acetal groups (scheme 1: steps d and e). The carbamoyl esters are represented in Tables I and II. The yields, physical data, elemental analyses are in Table III. NMR data of carbamate derivated of D-galactose are in Tables IV-VIII.*

Step a

Synthesis of the O-(N,N-*diethylcarbamoyl) esters 1b-4b and the* O-(N,N-*diethylthiocarbamoyl) esters 1c-4c*

The *O*-(*N,N*-diethylcarbamoyl) esters **1b-4b** were obtained by condensing **1a-4a** respectively with *N,N*-diethylcarbamoyl chloride in the presence of KOH in Me_2SO-toluene at 8°C (87–95% yield). The *O*-(*N,N*-dialkylthiocarbamoyl) esters **1c-4c** were prepared from the acetonides **1a-4a** and *N,N*-diethylthiocarbamoyl chloride using the same conditions but with the stronger base, potassium *t*-butoxide (83–87% yield). This modification was applied in order to increase the rate of the *O*-thiocarbamoylation which was slower than the rate of *O*-carbamoylation.

* The entire NMR data were leaved in reserve at the Editor's office.



a) X = O, $R_1 = R_2 = C_2H_5$, $(C_2H_5)_2NCOCl$, KOH, Me_2SO, toluene, 8 °C, 15 min, 81% ; X = S, $R_1 = R_2 = C_2H_5(C_2H_5)_2NCSCl$, *t*-BuOK, Me_2SO, toluene, 8 °C, 15 min, 85% ; X = O, $R_1 = C_2H_5$, R_2 = H, C_2H_5NCO, Et_3N, toluene, 45 °C, 72 h, 56% ; X = S, $R_1 = C_2H_5$, R_2 = H, C_2H_5NCS, DMAP, pyridine, 110 °C, 96 h, 31% ; b) I_2, PPh_3, imidazole, toluene, 110 °C, 180 min, 69% ; c) X = S, $R_1 = R_2 = C_2H_5$, $(C_2H_5)_2NCSSLi$, HMPA, toluene, 110 °C, 2 h, 87% ; d) 0.6M HCl, water, dioxane, 30 °C, 20-30 min, 70-88% ; d) 0.6M HCl, water, dioxane, 60 °C, 2 h, 50-70%.

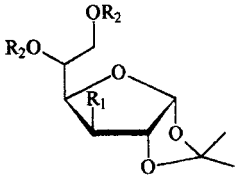
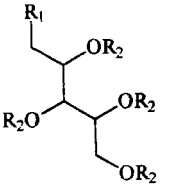
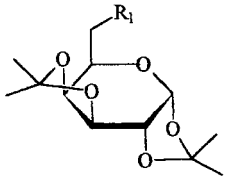
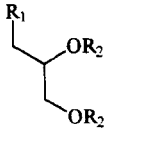
SCHEME 1

Synthesis of the O-*(*N-*ethylcarbamoyl) esters 1d-4d and the* O-*(*N-*ethylthiocarbamoyl) esters 1e-4e*

The *O*-(*N*-ethylcarbamoyl) esters **1d-4d** were obtained by condensing ethyl isocyanate and **1a-4a** respectively in the presence of triethylamine in toluene at 45 °C (56–98% yield). The same conditions with ethyl isothiocyanate and **1a-4a** respectively failed to give the desired *O*-(*N*-ethylthio-

carbamates). In contrast the *O*-(*N*-ethylthiocarbamoyl) esters **2e-4e** were successfully synthesized (83–91% yield) by increasing the reaction temperature (110 °C), increasing the concentrations of **2a-4a** respectively and using pyridine instead of triethylamine-toluene. However, it was found that the conversion of the diacetonide **1a** to the 3-*O*-(*N*-ethylthiocarbamoyl) ester **1e** (31% yield) required addition of 4-(dimethylamino) pyridine (DMAP) in pyridine. As might be expected, thioesterification proved to require more forcing conditions than at the primary position.

TABLE I

Compounds		*R_1*	*R_2*
		**a**= OH	$C(CH_3)_2$
		b = $OCONEt_2$	$C(CH_3)_2$
		c = $OCSNEt_2$	$C(CH_3)_2$
		d = OCONHEt	$C(CH_3)_2$
		d' = OCONEtMe	$C(CH_3)_2$
1	**3**	**e** = OCSNHEt	$C(CH_3)_2$
		f = $SCONEt_2$	$C(CH_3)_2$
		g = SCONHEt	$C(CH_3)_2$
		h = $SCSNEt_2$	$C(CH_3)_2$
		i = SCSNHEt	$C(CH_3)_2$
		**j** = $OCONEt_2$	H
		k = $OCSNEt_2$	H
		m = OCONHEt	H
2	**4**	**n** = OCSNHEt	H
		p = $SCSNEt_2$	H
		q = SCSNHEt	H

Steps b and c

Synthesis of the S-*(carbamoyl) esters 2f, 3g, 4f, 4g and the* S-*(thiocarbamoyl) esters 1h-4h, 2i-4i*

The starting materials **2a-4a** were first converted into the corresponding iodo-derivatives **2a'-4a'**[14] (69–85% yield) and reacted with *S*-(*N,N*-diethylcarbamoyl) and *S*-(*N*-ethylcarbamoyl) acid salts respectively in acetone at 56 °C to give the *S*-carbamates **2f, 4f, 3g** and **4g** (40–75% yield). In contrast, the iodide **1a'** formed in the same manner did not give the 3-*S*-(carbamoyl) esters **1f-1g** thus confirming the poor reactivity of the secondary hydroxyl group in **1a**. In a parallel study, the *S*-(*N,N*-diethylthiocarbamoyl) and *S*-(*N*-ethylthiocarbamoyl) acid salts[15] were reacted with **2a'-4a'**[14] to give the *S*-(*N,N*-diethylthiocarbamoyl) esters **2h-4h** and *S*-(*N*-ethylthiocarbamoyl) esters **2i-4i** (73–96% yield) respectively. In contrast neither 3-*S*-(*N,N*-diethylthiocarbamoyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1h**) nor 3-*S*-(*N*-ethylthiocarbamoyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1i**) were successfully formed from the iododiacetoneallose **1a'** using the above conditions. However, the *S-(N,N*-diethylthiocarbamate) **1h** was obtained by condensing iodo-derivative **1a'** with *S-(N,N*-diethylthiocarbamoyl) acid salt using HMPA-toluene at 110 °C (87% yield).

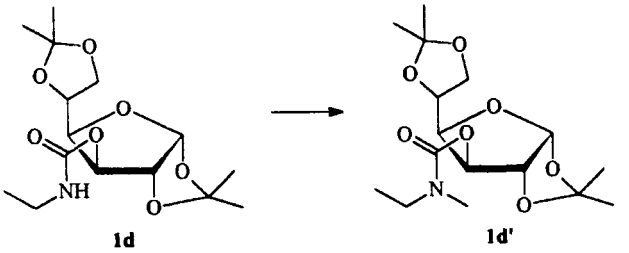
Steps d and e

Deprotection of the O-*(carbamoyl),* O-*(thiocarbamoyl),* S-*(carbamoyl), and* S-*(thiocarbamoyl) esters*

Selective partial acid-catalized deprotection of D-glucose derivatives **1b-1d** and **1h** in 1,4-dioxane-H_2O-HCl at 30 °C afforded the monoacetal compounds **1j-1m** and **1p** in yields ranging from 70 to 88%. Using the same conditions at 60 °C, total acid-catalized deprotection of derivatives **1b-1d, 1h, 2b-2e** and **2h, 3b-3d, 3h, 4b-4e, 4h-4i** gave the ester derivatives **5a-5i** and **3j-3m, 3p, 4j-4q** (30–120 min in 39–88%).

Synthesis of the O-(N-*ethyl*-N-*methylcarbamoyl) esters 1d'-4d'*

The *O*-(*N*-ethyl-*N*-methylcarbamoyl) esters **1d'-4d'** (scheme 2) were obtained (45–58% yield) by condensing **1d-4d** respectively with methyl iodide and NaOH in dioxane.

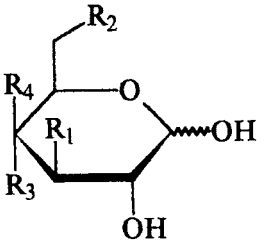


1d **1d'**

CH_3I, NaOH, dioxane, 24 h, 45%.

SCHEME 2

TABLE II

Compounds		R_1	R_2	R_3	R_4
	**a** =	$OCONEt_2$	OH	OH	H
	b =	$OCSNEt_2$	OH	OH	H
	c =	OCONHEt	OH	OH	H
	d =	$SCSNEt_2$	OH	OH	H
	e =	OH	$OCONEt_2$	H	OH
	f =	OH	$OCSNEt_2$	H	OH
	g =	OH	OCONHEt	H	OH
	h =	OH	OCSNHEt	H	OH
5	**i** =	OH	$SCSNEt_2$	H	OH

NMR spectra

The chemical shifts for the signals of the H-C group geminal to the (thio)ester is in character with a carbamoyl group. For example in the case of the diacetonegalactose derivatives **2b-2c**, **2f** and **2h** (Tables IV and VI), the *O*-carbamoyl ester **2b** showed a downfield shift for H-6 (ca. +0.4 ppm), H-6' (ca. +0.4 ppm), H-5 (ca. +0.2 ppm) and C-6 (ca. +2.0 ppm) along with an upfield shift for C-5 (ca. −1.6 ppm). These phenomena were amplified for H-6 (ca. +1.0 ppm), H-6' (ca. +0.7 ppm), H-5 (ca. +0.3 ppm), C-6 (ca. +8.0 ppm) and C-5 (ca. −1.7 ppm) of the *O*-thiocarbamoyl ester **2c**. The *S*-carbamoyl ester **2f** showed a downfield shift for H-5 (ca. +0.1

ppm) along with an upfield shift for H-6 (ca. –0.6 ppm), H-6' (ca. –0.7 ppm), C-5 (ca. –1.5 ppm) and C-6 (ca. –32.1 ppm). The *S*-thiocarbamoyl ester **2h** showed a downfield shift for H-5 (ca. +0.2 ppm) along with an upfield shift for H-6 (ca. –0.2 ppm), H-6' (ca. –0.4 ppm), C-5 (ca. -1.4 ppm) and C-6 (ca. –25.0 ppm).

Because of the high rotational energy barrier for the C-N bond, we observed the planar structure of the carbamoyl and thiocarbamoyl esters. The proton and carbon NMR data at 30 °C in Me_2SO-d_6 for the diacetonegalactose derivative **2d** which possesses an *O*-(*N*-ethylcarbamoyl) group showed the presence of one isomeric form. In contrast the proton and carbon NMR data at 30 °C in Me_2SO-d_6 for the diacetonegalactose esters **2d'**, **2e**, **2i** which possess *O*-(*N*-ethyl-*N*-methylcarbamoyl), *O*-(*N*-ethylthiocarbamoyl), *S*-(*N*-ethylthiocarbamoyl) groups respectively showed the presence of both *Z* and *E* forms. In the case of the carbamate **2d**, the free rotation about the C-N bond was observed at 30 °C. In the case of the thiocarbamates **2e** and **2i**, the methylene carbon and proton signals assigned to NCH_2 of the thiocarbamoyl group are indicative of the *Z* and *E* forms (^{13}C: **2e *Z*:** δ NCH_2 40.0 ppm and **2e *E***: δ NCH_2 38.2 ppm ; **2i *Z***: δ NCH_2 41.9 ppm and **2i *E***: δ NCH_2 41.1 ppm ; ^{1}H: **2e *Z***: δ NCH_2 3.50 ppm and **2e *E***: δ NCH_2 3.26 ppm ; **2i *Z***: δ NCH_2 3.62 ppm and **2i *E***: δ NCH_2 3.40 ppm) because the thiocarbonyl group anisotropy caused deshielding of NCH_2 in the *Z* form.[16]

The proton and carbon NMR data for compounds **2d'**, **2e**, and **2i** were obtained by following stepwise increases of 10 °C in temperature in the range 30 to 90 °C. The results noted in Tables VII and VIII showed that the *O*-(*N*-ethyl-*N*-methylcarbamate) **2d'** was a *Z*/*E* (1:1) mixture at 30–50°C and coalescence was observed at 70°C at which free rotation about the C-N bond occured. It is noteworthy that no trace of coalescence was obtained from 30 to 90°C with the *O*-(*N*-ethylthiocarbamate) **2e** and *S*-(*N*-ethylthiocarbamate) **2i** thus confirming that the rotational energy barrier was higher for thiocarbamates than for carbamates.[17–19]

Antifungal properties of some of the dithio-, thio- and carbamoyl esters had been studied against *Alternaria brassicae, Septoria nodorum, Pseudocercosporella herpotrichoides,* and *Phytophtora cinnamomi* using a solid medium (Czapek Yeast Agar, glycine, aga[20]) and a Fayret liquid medium (glucose, ammonium nitrate[21]). Among all the compounds tested, the six compounds **3j**, **4j**, **3k**, **4k**, **3p**, and **4p** compared to that of the commercial Carbendazime and Maneb had slight growth inhibition against the five fungi tested at 50, 20, and 2 ppm.

TABLE III Yields, physical data and elemental analyses

Compd	*% yield*	*mp (°C)*	*[α]d (°) in $CHCl_3$*	*MW*	*Elemental Analyses Calcd (found)*			
					C	*H*	*S*	*N*
1b	95	-	-38 (c 1.5, 22 °C)	359.42	56.81	8.13	-	3.90
					(56.84)	(8.18)	-	(3.98)
2b	90	49 – 50	-28 (c 1.6, 22 °C)	359.42	56.81	8.13	-	3.90
					(56.83)	(8.09)	-	(3.88)
3b	92	-	-	331.41	57.99	8.82	-	4.23
					(58.00)	(9.02)	-	(4.31)
4b	87	-	-	231.29	57.12	9.15	-	6.06
					(57.16)	(9.11)	-	(6.10)
1c	85	53 – 54	-69 (c 1.6, 22 °C)	375.49	54.38	7.78	8.54	3.73
					(54.25)	(7.90)	(8.38)	(3.71)
2c	87	-	-54 (c 1.2, 22 °C)	375.49	54.38	7.78	8.54	3.73
					(54.21)	(7.72)	(8.32)	(3.48)
3c	83	42 – 43	-	347.47	55.31	8.41	9.23	4.03
					(55.56)	(8.52)	(8.56)	(4.11)
4c	86	-	-	247.36	53.41	8.56	12.96	5.66
					(53.66)	(8.57)	(13.04)	(5.69)
1d	56	116 – 117	-36 (c 1.3, 20 °C)	331.37	54.37	7.60	-	4.23
					(54.39)	(7.65)	-	(4.27)
2d	97	-	-43 (c 1.2, 22 °C)	331.37	54.37	7.60	-	4.23
					(54.51)	(7.49)	-	(4.19)
3d	98	-	-	303.35	55.43	8.31	-	4.62
					(55.47)	(8.37)	-	(4.59)
4d	98	-	-	203.24	53.19	8.43	-	6.89
					(53.21)	(8.49)	-	(6.85)
1d'	45	79 – 82	+56 (c 1.5, 27 °C)	345.39	55.64	7.88	-	4.06
					(55.70)	(7.92)	-	(4.00)
2d'	58	-	-46 (c 1.0, 23 °C)	345.39	55.64	7.88	-	4.06
					(55.72)	(7.90)	-	(4.08)
3d'	45	-	-	317.38	56.77	7.88	-	4.41
					(56.82)	(7.85)	-	(4.45)
4d'	54	-	-	217.26	55.28	8.81	-	6.45

Compd	% yield	mp (°C)	[α]d (°) in $CHCl_3$	MW	Elemental Analyses Calcd (found)			
					C	H	S	N
					(55.32)	(8.92)	-	(6.42)
1e	31	-	-43 (c 1.1, 22 °C)	347.43	51.86	7.25	9.23	4.03
					(51.98)	(7.31)	(9.51)	(4.00)
2e	91	117 – 119	-51 (c 1.4, 22 °C)	347.43	51.86	7.25	9.23	4.03
					(51.67)	(7.23)	(9.17)	(3.97)
3e	87	-	-	319.42	52.64	7.84	10.04	4.39
					(52.37)	(7.91)	(9.98)	(4.43)
4e	83	-	-	219.30	49.29	7.81	14.62	6.39
					(48.97)	(7.95)	(15.01)	(6.42)
2f	40	-	-19 (c 1.0, 26 °C)	375.49	54.38	7.78	8.54	3.73
					(53.99)	(7.82)	(8.76)	(3.68)
4f	72	-	-	247.36	53.41	8.56	12.96	5.66
					(53.45)	(8.32)	(13.20)	(5.72)
3g	72	-	-	319.42	52.64	7.89	10.04	4.39
					(52.35)	(7.84)	(10.24)	(4.27)
4g	75	-	-	219.30	49.29	7.81	14.62	6.39
					(49.02)	(7.95)	(14.32)	(6.41)
1h	87	83 – 85	-44 (c 1.5, 20 °C)	391.55	52.15	7.46	16.38	3.58
					(52.15)	(7.48)	(16.57)	(3.62)
2h	87	84 – 86	-15 (c 1.9, 20 °C)	391.55	52.15	7.46	16.38	3.58
					(52.13)	(7.42)	(16.21)	(3.55)
3h	94	72 – 74	-	363.54	52.86	8.04	17.64	3.85
					(52.83)	(8.11)	(17.55)	(3.91)
4h	96	-	-	263.42	50.16	8.03	24.35	5.32
					(50.23)	(8.11)	(24.60)	(5.27)
2i	88	-	-38 (c 1.5, 22 °C)	363.50	49.56	6.93	17.64	3.85
					(49.62)	(6.97)	(17.96)	(3.85)
3i	73	-	-	335.49	50.12	7.51	19.12	4.18
					(50.06)	(7.65)	(18.99)	(4.19)
4i	95	-	-	235.37	45.93	7.28	27.25	5.95
					(45.97)	(7.32)	(27.14)	(5.91)
1j	70	-	+64 (c 1.4, 22 °C)[a]	319.35	52.65	7.89	-	4.39

Compd	*% yield*	*mp (°C)*	*[α]d (°) in $CHCl_3$*	*MW*	*Elemental Analyses Calcd (found)*			
					C	*H*	*S*	*N*
					(52.59)	(8.02)		(4.37)
3j	85	-	-	251.28	47.80	8.42	-	5.57
					47.82)	(8.38)		(5.39)
4j	79	-	-	191.23	50.25	8.96	-	-7.32
					(50.23)	(8.79)		(7.19)
1k	88	84 – 86	+64 (c 1.4, 22 °C)[a]	335.42	50.13	7.51	9.56	4.18
					(50.21)	(7.63)	(10.05)	(4.30)
3k	65	66 – 68	-	267.35	44.93	7.92	11.99	5.24
					(44.59)	(7.91)	(11.57)	(5.14)
4k	95	-	-	207.29	46.35	8.27	15.47	6.76
					(46.40)	(8.35)	(15.15)	(6.42)
1m	73	112 – 114	+50 (c 1.1, 25 °C)[a]	291.30	49.48	7.25	-	4.81
					(49.37)	(7.21)		(4.67)
3m	80	77 – 79	-	223.23	43.05	7.68	-	6.27
					(42.68)	(7.49)		(6.24)
4m	71	-	-	163.17	44.17	8.03	-	8.58
					(43.29)	(8.32)		(8.39)
4n	57	-	-	179.24	40.21	7.31	17.89	7.81
					(40.51)	(7.56)	(17.54)	(7.57)
1p	75	78 – 80	+91 (c 1.2, 22 °C)[a]	351.49	47.84	7.17	18.25	3.98
					(47.75)	(7.25)	(18.91)	(4.02)
3p	60	-	-	283.41	42.38	7.47	22.63	4.94
					(42.51)	(7.51)	(23.01)	(5.08)
4p	85	-	-	223.36	43.02	7.67	28.71	6.27
					(42.98)	(7.82)	(29.37)	(6.30)
4q	55	-	-	195.31 1	36.90	6.71	32.84	7.17
					(36.95)	(6.87)	(31.99)	(7.06)
5a	85	107 – 109	+21 (c 1.1, 22 °C)[a]	279.29	47.31	7.58	-	5.02
					(47.56)	(7.50)		(5.14)
5b	75	-	-38 (c 1.5, 22 °C)[a]	295.35	44.73	7.17	10.86	4.74
					(44.79)	(7.05)	(12.09)	(4.91)
5c	84	109 – 111	+36 (c 1.2, 20 °C)[a]	251.24	43.03	6.82	-	5.58

Compd	% yield	mp (°C)	[α]d (°) in $CHCl_3$	MW	Elemental Analyses Calcd (found)			
					C	H	S	N
					(43.09)	(6.59)		(5.37)
5d	50	-	+71 (c 1.2, 22 °C)[a]	311.42	42.42	6.80	20.59	4.50
					(42.46)	(6.75)	(21.06)	(4.49)
5e	85	126 – 128	+66 (c 1.1, 25 °C)[a]	279.29	47.31	7.58	-	5.02
					(47.30)	(7.55)		(5.05)
5f	62	129 – 132	-38 (c 1.5, 22 °C)[a]	295.35	44.73	7.17	10.86	4.74
					(44.68)	(7.15)	(10.51)	(4.72)
5g	88	127 – 129	-47 (c 1.9, 20 °C)[a]	251.24	43.03	6.82	-	5.58
					(43.15)	(6.78)		(5.55)
5h	39	-	+26 (c 1.5, 20 °C)[a]	267.30	40.44	6.41	12.00	5.24
					(41.06)	(6.38)	(12.06)	(5.13)
5i	60	-	+53 (c 1.1, 20 °C)[a]	311.42	42.42	6.80	20.59	4.50
					(42.38)	(6.82)	(20.05)	(4.53)

a. Optical rotations were measured in CH_3OH.

EXPERIMENTAL

Melting points were determined on a digital melting-point apparatus (Electrothermal) and are uncorrected. Optical rotations were recorded at 22 °C in $CHCl_3$ or MeOH solutions with a digital polarimeter DIP-370 (JASCO) using a 1dm cell. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or Me_2SO-d_6 (internal Me_4Si) respectively at 300.13 MHz and at 75.47 MHz (Bruker AM WB-300). TLC was performed on Silica F254 (Merck) and detection by UV light at 254 nm or by charring with phosphomolybdic-H_2SO_4 reagent. Column chromatography was effected on Silica Gel 60 (Merck, 230 mesh). Me_2CO, hexane, ether and each industrial grade were supplied by CINAS. Elemental analyses were performed by the Service Central de Micro-Analyse du Centre National de Recherche Scientifique (Vernaison, France). *N,N*-diethylcarbamoyl chloride, ethyl isocyanate, ethyl isothiocyanate, bases and solvents were supplied by JANSSEN or ALDRICH.

TABLE IV ^{1}H NMR chemical shifts (δ in ppm, in $CDCl_3$) for compounds **2b-2f** and **2h-2i**

Compd	*Chemical shifts (δ)*											
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6'*	*C(CH$_3$)$_2$*				*Others*
2b	5.46	4.25	4.53	4.17	3.97	4.20	4.06	1.42	1.38	1.25	1.25	2.84 (4H, NCH_2), 1.03 (6H, CH_3)
2c	5.46	4.24	4.55	4.20	4.11	4.80	4.35	1.42	1.38	1.25	1.25	3.74,3.50,3.34(4H,NCH_2), 1.03 (6H, CH_3)
2d	5.44	4.34	4.60	4.21	3.90	4.04	3.90	1.40	1.34	1.28	1.27	2.98(2H,NCH_2),0.99(3H, CH_3)
2d'	5.46	4.25	4.55	4.18	3.98	4.22	4.08	1.44	1.38	1.27	1.26	3.25 (2H, NCH_2), 1.05 (3H, CH_3), 2.82 (3H, NCH_3)
2e(*Z*)	5.47	4.26	4.55	4.21	4.13	4.73	4.34	1.45	1.39	1.27	1.26	3.50(2H,NCH_2), 1.14(3H,CH_3)
2e(*E*)	5.47	4.26	4.56	4.21	4.13	4.78	4.42	1.45	1.39	1.27	1.26	3.26(2H,NCH_2), 1.11 (3H,CH_3)
2f	5.46	4.22	4.54	4.24	3.88	3.14	2.93	1.42	1.39	1.29	1.25	3.30,3.93 (4H,NCH_2),1.10(6H,CH_3)
2h	5.38	4.17	4.50	4.22	4.01	3.55	3.24	1.44	1.44	1.24	1.19	3.97,3.83,3.66(4H,NCH_2),1.15,1.13(6H,CH_3)
2i(*Z*)	4.42	4.21	4.53	4.21	3.98	3.36	3.21	1.40	1.37	1.26	1.22	3.62(2H,NCH_2), 1.43 (3H, CH_3)
2i(*E*)	5.42	4.21	4.53	4.21	4.08	3.41	3.32	1.40	1.37	1.26	1.22	3.40(2H,NCH_2),1.40(3H,CH_3)

1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (**1a**), 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**2a**), 1,2:3,4-di-*O*-isopropylidene-DL-xylitol (**3a**), 1,2-*O*-isopropylidene-DL-glycerol (**4a**) were synthesized in accordance with previous works.[22]

3-Deoxy-3-iodo-1,2: 5,6-di-*O*-isopropylidene-α-D-allofuranose (**1a'**), 6-deoxy-6-iodo-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**2a'**), 5-deoxy-5-iodo-1,2:3,4-di-*O*-isopropylidene-DL-xylitol (**3a'**), 3-deoxy-3-iodo-1,2-*O*-isopropylidene-DL-glycerol (**4a'**) were synthesized in accordance with the method described by Garegg.[14]

S-(N-*Ethylcarbamic acid*) *sodium salt*: NaHS (19.7 g, 0.35 mol) was added to a stirred solution of ethylisocyanate (5.0 g, 70.4 mmol) in 1,4-dioxane-water (1:1) for 15 min. Diethyl ether was added and the S-(N-ethylcarbamic acid) sodium salt (2.6 g, 29%) was filtered.

S-(N,N-Diethylthiocarbamic acid) lithium salt: CS_2 (10.6 g, 0.14 mol) was added to a stirred solution of diethylamine (10.0 g, 0.14 mol) in acetone at 8 °C. The mixture was stirred for 10 min, and $LiOH.H_2O$ (5.9 g, 0.14 mol) was added. Stirring was continued to 15 min and the reaction mixture was concentrated under reduced pressure. The crude product was recrystallized from 1,4-dioxane to yield 18.2 g-86%) of *S-(N,N*-diethylthiocarbamic acid) lithium salt.

S-(N-*Ethylthiocarbamic acid*) *lithium salt*: The above method applied to ethylamine yielded the corresponding *S-(N*-ethylthiocarbamic acid) lithium salt in 72%.

All the carbamoyl esters were synthesized by a similar route and therefore for brivety the synthetic procedures for representative derivatives are described below. Yields and analytical details are summarized in Tables III-VIII.

O-(N,N-*Diethylcarbamoyl*) esters **1b-4b** - *General Procedure*: *N,N*-Diethylcarbamoyl chloride (22.9 mmol) was added dropwise to a stirred solution of **1a-4a** (19.2 mmol) and KOH (38.5 mmol) in Me_2SO-toluene (5:95, 50 mL) at 8 °C for 15 min. Ammonium chloride in aqueous solution was added and the mixture stirred for a further 10 min. The organic extract was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude product was purified on a silica gel column eluted with hexane-acetone to give **1b-4b**.

O-(N,N-*Diethylthiocarbamoyl*) *esters* **1c-4c** - *General Procedure*: To a stirred solution of thiophosgene (25.2 mmol) in toluene (27 mL) at 8 °C was added diethylamine (50.4 mmol) dropwise in toluene (8 mL). At the

end of the addition, the diethylammonium chloride was removed by filtration. The filtrate (26 mL) was added dropwise to a stirred mixture of **1a-4a** (19.2 mmol) and potassium *t*-butoxide (23.0 mmol) in Me_2SO-toluene (13:87, 15 mL) below 8 °C for 15 min. Ammonium chloride in aqueous solution was added and the mixture stirred for a further 10 min. The organic extract was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude product was purified on a silica gel column eluted with hexane-acetone (9:1) to give **1c-4c**.

O-(N-*Ethylcarbamoyl*) *esters* **1d-4d** - *General Procedure*: Ethyl isocyanate (23.0 mmol) was added dropwise to a stirred solution of **1a-4a** (19.2 mmol) and triethylamine (23.0 mmol) in toluene (50 mL) at 45 °C for 24–72 h. The organic mixture was concentrated under reduced pressure. The crude product was purified on a silica gel column eluted with hexane-acetone to give **1d-4d**.

O-(N-*Ethyl*-N-*methylcarbamoyl*) *esters* **1d'-4d'** - *General Procedure*: Methyl iodide (5.4 mmol) was added dropwise to a stirred solution of **1d-4d** (4.5 mmol) and NaOH (9 mmol) in 1,4-dioxane at room temperature for 24 h. Ammonium chloride in aqueous solution was added and the mixture stirred for a further 10 min. The organic extract was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude product was purified on a silica gel column eluted with hexane-acetone to give **1d'-4d'**.

O-(N-*Ethylthiocarbamoyl*) *esters* **2e-4e** - *General Procedure*: Ethyl isothiocyanate (38.5 mmol) was added dropwise to a stirred solution of **2a-4a** (19.2 mmol) and triethylamine (23.0 mmol) in pyridine (10 mL) at 110 °C for 24–96 h. The organic mixture was concentrated under reduced pressure. The crude product was purified on a silica gel column eluted with hexane-acetone to give **2e-4e**.

3-O-(N-*Ethylthiocarbamoyl*)-*1;2:5,6-di*-O-*isopropylidene*-α-*D-glucofuranose* (**1e**): Ethyl isothiocyanate (3.3 g, 38.5 mmol) was added dropwise to a stirred solution of **1a** (5.0 g, 19.2 mmol) and DMAP (4.7 g, 38.5 mmol) in pyridine (5 mL) at 110 °C for 96 h. The organic mixture was concentrated under reduced pressure. The crude product was purified on a silica gel column eluted with hexane-acetone (9:1) to give 2.1 g (31%) of **1e** as a Z/E (7:3) mixture.

S-(N,N-*Diethylcarbamoyl*) *esters* (**2f, 4f**) - *General Procedure*: A solution of diethylamine (8.1 mmol) and $LiOH.H_2O$ (8.1 mmol) in acetone (10 mL) was stirred at 0 °C for 10 min. COS was bubbled through the mixture

maintained at 0 °C for 30 min. $N_2$was then bubbled for a further 10 min. The iodo-derivatives **2a'** and **4a'** (5.4 mmol) was added dropwise to the stirred solution of *S*-(*N,N*-diethylcarbamic acid) lithium salt at 56 °C for 24 h. The mixture was cooled at room temperature and a solution of hexane-water (1:1) (200 mL) was added. The aqueous phase was extracted with hexane-diethyl ether (1:1) (100 mL), the organic phases were washed twice with water and dried (Na_2SO_4). The crude product was purified on a silica gel column eluted with hexane-acetone to give **2f** and **4f**.

TABLE V ^{1}H NMR coupling constances (J in Hz, in $CDCl_3$) for compounds **2b-1f** and **2h-2i**

Compd	*Coupling constances (Hz)*							
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	NCH_2CH_3
2b	4.9	2.4	8.0	1.5	-	7.4	11.8	7.1
2c	4.9	2.5	7.9	1.8	3.3	8.2	11.6	6.9
2d	5.0	2.2	8.0	-	6.4	5.6	8.3	7.1
2d'	4.9	2.5	7.9	1.7	-	7.8	11.3	7.1
2e(*Z*)	4.9	2.3	7.8	1.6	3.6	8.1	11.6	7.3
2e(*E*)	4.9	2.4	7.8	1.6	3.5	8.2	11.6	7.3
2f	4.9	2.4	7.9	1.8	4.5	8.7	13.9	7.1
2h	4.9	2.3	7.9	1.5	4.5	8.5	14.1	6.2
2i(*Z*)	4.9	2.3	7.9	-	4.6	8.5	14.6	7.2
2i(*E*)	4.9	2.3	7.9	-	6.2	4.3	14.1	7.2

S-(N-*Ethylcarbamoyl*) *esters* **(3g, 4g)** - *General Procedure*: A solution of iododerivatives **3a'** and **4a'** (20.7 mmol) and *S*-(*N*-ethylcarbamic acid) sodium salt (31.0 mmol) in acetone (70 mL) was stirred at 56 °C for 24 h. The mixture was cooled at room temperature and a solution of hexane-water (1:1) (200 mL) was added. The aqueous phase was extracted with hexane-diethyl ether (1:1) (100 mL). The organic phases were washed twice with water and dried (Na_2SO_4). The crude product was purified on a silica gel column eluted with hexane-acetone to give **3g** and **4g**.

TABLE VI ^{13}C NMR chemical shifts (δ in ppm, in $CDCl_3$) for compounds **2b-2f** and **2h-2i**

Compd	*Chemical shifts (δ)*												
	C-1	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*$C(CH_3)_2$*		*$C(CH_3)_2$*				*Others*
2b	96.2	70.5	70.7	71.2	66.6	64.0	109.5	107.7	25.9	25.9	25.0	24.3	155.1 (CO), 41.9, 41.5 (2C, NCH_2), 13.9, 13.5 (2C, CH_3)
2c	96.3	70.6	70.7	71.2	69.7	66.5	109.5	108.6	25.9	25.9	25.0	24.3	187.0(CS),47.7,43.5 (2C,NCH_2), 13.1, 11.8 (2C, CH_3)
2d	95.5	69.7	70.0	70.3	65.7	62.9	108.4	107.8	25.7	25.6	24.7	24.2	155.8 (CO),34.9(NCH_2),14.8(CH_3)
2d'	96.1	70.5	70.6	71.1	66.4	64.1	109.3	108.5	25.8	25.8	24.8	24.3	155.7 (CO), 43.5 (NCH_2), 12.5 (CH_3), 33.7, 33.2 (NCH_3)
2e(*Z*)	96.3	70.4	70.7	71.1	66.2	68.7	109.6	108.7	25.9	25.9	24.9	24.4	189.8(CS),40.0(NCH_2),13.6(CH_3)
2e(*E*)	96.3	70.4	70.7	71.1	66.2	70.3	109.6	108.7	25.9	25.9	24.9	24.4	189.8(CS),38.2(NCH_2), 14.2 (CH_3)
2f	96.6	70.6	71.0	72.3	67.6	30.7	109.3	108.6	25.9	25.8	25.0	24.4	166.7 (CO),42.0(NCH_2),13.3(CH_3)
2h	96.4	70.6	70.9	72.4	66.8	36.9	109.2	108.7	25.9	25.9	25.0	24.4	195.2 (CS), 49.3, 46.7 (2C, NCH_2), 12.4, 11.4 (2C, CH_3)
2i(*Z*)	96.4	70.5	70.9	72.2	67.6	35.5	109.3	108.9	25.9	25.9	24.9	24.3	196.7 (CS),41.9(NCH_2), 13.3 (CH_3)
2i(*E*)	96.4	70.5	70.9	72.2	66.7	36.1	109.3	108.9	25.9	25.9	24.9	24.3	196.7 (CS),41.1(NCH_2),13.9(CH_3)

TABLE VII ^{1}H NMR chemical shifts (δ in ppm, in Me_2SO-d_6) for compound **2d'**

Temp (°C)	*Chemical shifts* (δ)											
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6'*	*C(CH$_3$)$_2$*				*Others*
30	5.44	4.34	4.62	4.08	3.96	4.24	3.99	1.41	1.35	1.28	1.27	3.23(4H,NCH_2), 1.03 (6H, CH_3), 2.80(3H,NCH_3)
70	5.44	4.32	4.60	4.11	3.96	4.25	4.04	1.43	1.37	1.30	1.29	3.24(4H,NCH_2),1.05(6H,CH_3),2.81(3H,NCH_3)

TABLE VIII ^{13}C NMR chemical shifts (δ in ppm, in Me_2SO-d_6) for compound **2d'**

Temp (°C)	*Chemical shifts* (δ)												
	C-1	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C(CH$_3$)$_2$*		*C(CH$_3$)$_2$*				*Others*
30	95.5	69.8	70.3	70.3	65.9	63.7	108.5	107.8	25.7	25.6	24.8	24.1	155.0(CO),42.9(NCH_2),12.5,12.2 (CH_3), 33.5, 32.8 (NCH_3)
40	95.5	69.8	70.3	70.3	65.9	63.7	108.5	107.8	25.7	25.6	24.8	24.1	155.0(CO),42.9(NCH_2),12.5,12.2 (CH_3), 33.5, 32.8 (NCH_3)
50	95.5	69.8	70.0	70.3	65.9	63.7	108.5	107.8	25.7	25.6	24.8	24.1	155.0 (CO),42.9 (NCH_2), 12.5, 12.2 (CH_3), 33.5, 32.8 (NCH_3)
60	95.5	69.9	70.1	70.4	65.9	63.7	108.6	107.8	25.8	25.6	24.8	24.2	155.1 (CO),42.9(NCH_2),12.3(1,CH_3), 33.1 (1, NCH_3)
70	95.5	70.0	70.1	70.4	66.0	63.8	108.6	107.8	25.8	25.6	24.8	24.2	155.1 (CO),42.9(NCH_2),12.3(CH_3), 33.1 (NCH_3)

S-(N,N-*Diethylthiocarbamoyl) esters* **2h-4h** - *General Procedure:* The above method applied to **2a'-4a'** and *S*-(*N,N*-diethylthiocarbamic acid) lithium salt yielded **2h-4h**.

Synthesis of S-(N-*Ethylthiocarbamoyl*) *esters* ***2i-4i*** - *General Procedure*: The above method applied to **2a'-4a'** and *S*-(*N*-ethylthiocarbamic acid) lithium salt yielded **2i-4i**.

3-S-(N,N-*Diethylthiocarbamoyl*)-*1,2:5,6-di*-O-*isopropylidene*-α-*D-glucofuranose* (**1h**): A solution of 3-deoxy-3-iodo-1,2: 5,6-di-O-isopropylidene-α-D-allofuranose (27.0 mmol) and *N,N*-diethyldithiocarbamic acid lithium salt (40.5 mmol) in HMPA-toluene (1:1) (5 mL) was stirred at 110 °C for 2 h. The mixture was cooled at room temperature and a solution of hexane-water (1:1) (200 mL) was added. The aqueous phase was extracted with hexane-diethyl ether (1:1) (100 mL), the organic phases were washed twice with water and dried (Na_2SO_4). The crude product was purified on a silica gel column eluted with hexane-acetone (9:1) to give 9.2 g (87%) of **1h**.

Carbamoyl esters **1j-1m** and **1p** - *General Procedure*: Carbamoyl esters **1b-1d** and **1h**(19.5 mmol) was reacted with a solution of 0.6M HCl in water-1,4-dioxane (1:9) (200 mL) at 30 °C for 20 min. After addition of sodium hydrogen carbonate (pH 6), the mixture was stirred 10 min, filtered and the solvent was removed under reduced pressure. The crude product was purified on a silica gel column eluted with hexane-acetone to give **1j-1m** and **1p**.

Carbamoyl esters **3j-3m**, **3p**, **4j-q** *and* **5a-i** - *General Procedure*: The above method applied to **1b-d**, **1h**, **2b-e**, **2h**, **3b-d**, **3h**, **4b-e** and **4h-i** at 60 °C for 30–120 min gave **3j-3m**, **3p**, **4j-q** and **5a-i**.

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