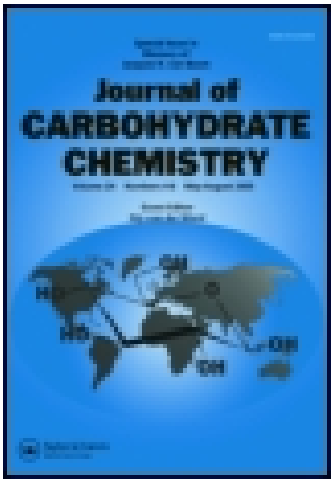

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Synthesis of Bis(Carbamoyl Ester) Derivatives of D-Glucose as Antifungal Products

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SYNTHESIS OF BIS(CARBAMOYL ESTER) DERIVATIVES OF D-GLUCOSE AS ANTIFUNGAL PRODUCTS

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ABSTRACT

Regiospecific carbamoylation of di-*O*-isopropylidene protected D-glucose gave a series of carbamoyl, thiocarbamoyl and dithiocarbamoyl esters at the C-3 secondary site. These were partially and fully deprotected to give two series of derivatives such that a choice of the extent of hydrophilic character could be made. The partially protected products were further derivatized regioselectively with a second carbamoyl, thiocarbamoyl or dithiocarbamoyl group at the C-6 primary site. We also report on antifungal properties of some of those compounds.

INTRODUCTION

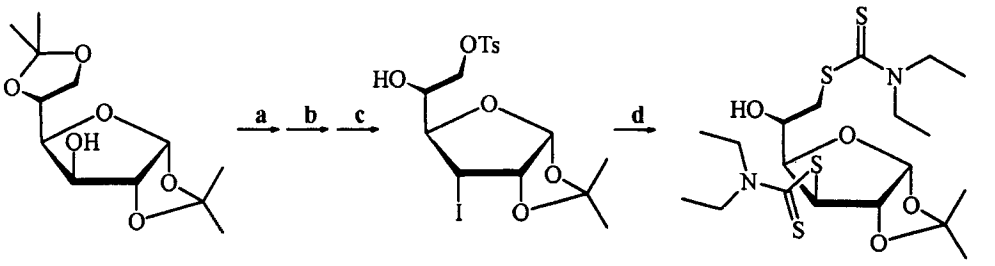
Carbamates are important in various areas of medicinal chemistry.[1-4] Also *N*-alkylcarbamoyl and *N,N*-dialkylcarbamoyl esters are in current use as pesticides[5] insecticides,[6,7] fungicides,[8,9] and herbicides.[10] These series include dithiocarbamic acid salts as well as carbamoyl, thiocarbamoyl and dithiocarbamoyl esters. Their biological properties vary in accordance with the type of carbamoyl group[11] (thiocarbamate and dithiocarbamate) such as when either or both oxygen atoms are replaced by sulphur atoms and when the nitrogen atom has one or two alkyl groups. We previously demonstrated[12]

that compounds with multiple substitutions of carbamoyl groups on a low molecular weight polyol such as glycerol (1,3-dideoxy-bis-1,3-*S*-(*N*,*N*-diethyldithiocarbamoyl)-glycerol) showed enhanced antifungal activity whilst having low toxicity (in contrast to many dithiocarbamic acid salts which release trace toxic metals[13]). This encouraging result led us to explore the synthesis of bis(carbamoyl esters) of carbohydrates with the objective of obtaining less hazardous and more environmentally friendly compounds. D-Glucose was chosen as the carbohydrate moiety since it is cheap and can be readily protected to permit: (i) a one-step bis-carbamoylation; (ii) both regiospecific carbamoylation at the secondary C-3 position and regioselective esterification at the primary C-6 position; (iii) a modulation of the hydrophilic-lipophilic balance (HLB) by choice of the number of free hydroxyl groups remaining in the final product; (iv) a convenient choice of either furanose or pyranose derivatives. This approach conveniently allows the preparation of a large range of biscarbamates in which the two carbamoyl groups may be the same or different. Antifungal activities of some derivatives are reported.

RESULTS AND DISCUSSION

The range of bis(carbamoyl esters) reported in this paper are synthesized from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1**). This starting material has provided convenient access to such products using two strategies. In the first strategy, the diesterification is effected in a one-step reaction following deprotection of the 5,6-isopropylidene group and consequent activation at both the 3- and 6- positions on 1,2-*O*-isopropylidene-α-D-glucofuranose. In the second strategy, the first ester group is attached at the C-3 position of the diacetoneglucose and the second, identical or not, is attached regiospecifically or regioselectively at the C-6 position, after 5,6- acetal deprotection.

Synthesis of bis(dithiocarbamoyl esters) by one-step biscarbamoylation. (Scheme 1) The key intermediate in the synthesis of the bisdithiocarbamates is the 3-iodo-6-*O*-tosyl-derivative **1'**. This was prepared by first converting compound **1** into the corresponding 3-iodo-derivative,[14] deprotecting the 5,6- acetal group and finally regioselectively tosylating the 6-OH group. The diactivated compound **1'** was reacted



1 1' 2

a) I_2, PPh_3, imidazole, toluene, 110 °C, 180 min, 69%; b) 0.6M HCl, water, dioxane, 30 °C, 30 min, 64%; c) *p*-toluenesulphonyl chloride, pyridine, toluene, 4 °C, 48 h, 84%; d) $(C_2H_5)_2NCSSLi$, HMPA, toluene, 110 °C, 24 h, 60%.

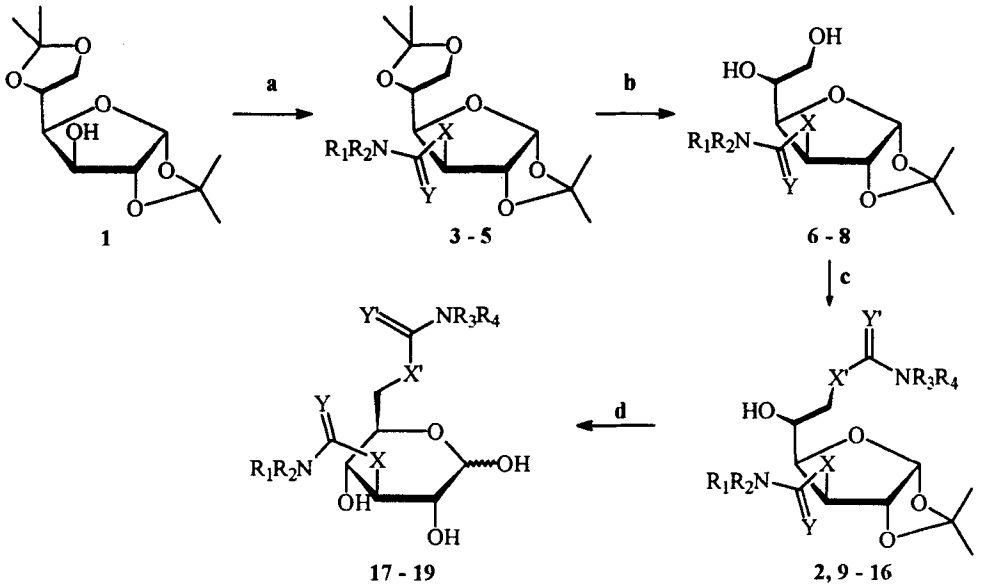
Scheme 1

with excess lithium *N,N*-diethyl dithiocarbamate[15] in HMPA-toluene (1:1) at 110 °C to give the bis(*N,N*-diethyldithiocarbamoyl ester) **2** (24 h, 60%). NMR data are in Tables 1-3.

General synthesis of bis(carbamoyl esters) by successive carbamoylations. Biscarbamate derivatives with two identical or different carbamoyl groups were synthesized in either three or four steps from compound **1** (Scheme 2). The hydrophilic character can be increased by deprotection of the remaining 1,2- acetal group in the final step of the synthesis. NMR data of obtained products are in Tables 1-4.

Step a: The 3-*O*-(*N,N*-diethylcarbamoyl) ester **3** was obtained by condensing compound **1** with *N,N*-diethylcarbamoyl chloride (1.2 equiv) in the presence of finely powdered KOH (2 equiv) in Me_2SO-toluene (5:95) at 8 °C (15 min in 81% yield). Using the same conditions, the rate of the reaction leading to the 3-*O*-(*N,N*-diethylthiocarbamoyl) ester **4** from the corresponding diacetonide **1** and *N,N*-diethylthiocarbamoyl chloride was slow, hence potassium *t*-butoxide was used instead of KOH to obtain product **4** with an improved yield (85%) and in a shorter reaction time (15 min *vs* 5 h).

The 3-*S*-(*N,N*-diethyldithiocarbamoyl) ester **5** was obtained, in 87% yield, by first converting compound **1** into 3-deoxy-3-iodo-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose followed by (S_N2) reaction with lithium dithiocarbamate (1.5 equiv) using similar conditions used for the preparation of the diester **2**.



2 ; 17 : X = X' = Y = Y' = S ; $R_1 = R_2 = R_3 = R_4 = CH_2CH_3$
3 ; 6 : X = Y = O ; $R_1 = R_2 = CH_2CH_3$
4 ; 7 : X = O ; Y = S ; $R_1 = R_2 = CH_2CH_3$
5 ; 8 : X = Y = S ; $R_1 = R_2 = CH_2CH_3$
9 ; 18 : X = X' = Y = Y' = O ; $R_1 = R_2 = R_3 = R_4 = CH_2CH_3$
10 : X = X' = Y' = O ; Y = S ; $R_1 = R_2 = R_3 = R_4 = CH_2CH_3$
11 : X = X' = Y = Y' = O ; $R_1 = R_2 = R_3 = CH_2CH_3$; R_4 = H
12 : X = X' = Y' = O ; Y = S ; $R_1 = R_2 = R_3 = CH_2CH_3$; R_4 = H
13 : X = Y = S ; X' = Y' = O ; $R_1 = R_2 = R_3 = CH_2CH_3$; R_4 = H
14 : X = X' = Y = O ; Y' = S ; $R_1 = R_2 = R_3 = CH_2CH_3$; R_4 = H
15 ; 19 : X = Y = O ; X' = Y' = S ; $R_1 = R_2 = R_3 = R_4 = CH_2CH_3$
16 : X = O ; Y = X' = Y' = S ; $R_1 = R_2 = R_3 = R_4 = CH_2CH_3$

a) X = Y = O, $(C_2H_5)_2NCOCl$, KOH, Me_2SO, toluene, 8 °C, 15 min, 81%; X = O, Y = S, $(C_2H_5)_2NCSCl$, *t*-BuOK, Me_2SO, toluene, 8 °C, 15 min, 85%; X = Y = S, $(C_2H_5)_2NCSSLi$, HMPA, toluene, 110 °C, 2 h, 87%; b) 0.6M HCl, water, dioxane, 30 °C, 20 - 30 min, 70 - 88%; c) X' = Y' = O, $(C_2H_5)_2NCOCl$, KOH, toluene, 0 °C, 2.3 - 2.6 h, 52 - 69%; X' = Y' = O, R_1 = H , C_2H_5NCO, pyridine, 40 °C, 48 - 72 h, 91 - 98%; X' = O, Y' = S, R_1 = H , C_2H_5NCS, pyridine, 40 °C, 96 h, 98%; X = Y = S, $(C_2H_5)_2NCSSLi$, acetone, 56 °C, 1 - 4.5 h, 72 - 89%; d) 0.6M HCl, water, dioxane, 60 °C, 2 h, 50 - 70%.

Scheme 2

Table 1: ^{1}H NMR Chemical Shifts (δ in ppm, in $CDCl_3$) for Compounds **1'** and **2 - 16**.

Compd	Chemical shifts (δ)											Others
	H-1	H-2	H-3	H-4	H-5	H-6	H-6'	$C(CH_3)_2$				
1'	5.71	4.53	4.15	4.15	4.15	4.15	3.68	1.48	1.30			7.75 (H-ortho), 7.30 (H-meta)
2	5.71	4.67	4.69	4.35	4.05	3.86	3.86	1,46	1.22			3.91, 3.87 (4H, NCH_2), 1.17, 1.15 (6H, CH_3)
3	5.76	4.50	5.04	4.13	4.14	4.00	3.91	1.42	1.31	1.23	1.20	3.17 (4H, NCH_2), 1.16, 1.10 (6H, CH_3)
4	5.76	4.68	5.60	4.14	4.15	4.01	3.91	1.44	1.31	1.22	1.20	3.82, 3.64 (4H, NCH_2), 1.16, 1.10 (6H, CH_3)
5	5.73	4.50	4.68	4.34	4.16	4.00	3.91	1.47	1.33	1.24	1.24	3.93 (2H, NCH_2), 3.65, 3.64 (2H, NCH_2), 1.21, 1.19 (6H, CH_3)
6	5.83	4.47	4.89	4.04	3.57	3.57	3.36	1.40	1.23			3.19 (4H, NCH_2), 1.05 (6H, CH_3)
7	5.86	4.58	5.98	4.15	3.56	3.85	3.66	1.48	1.28			3.78, 3.71, 3.42 (4H, NCH_2), 1.21, 1.14 (6H, CH_3)
8	5.68	4.67	4.74	4.30	3.67	3.79	3.57	1.44	1.23			3.92 (2H, NCH_2), 3.78, 3.73 (2H, NCH_2), 1.20, 1.17 (6H, CH_3)
9	5.84	4.43	5.02	4.03	3.58	4.30	3.99	1.31	1.13			3.10 (8H, NCH_2), 0.95, 0.91 (18H, CH_3)
10	5.77	4.58	5.81	4.15	3.71	4.38	4.08	1.39	1.20			3.76, 3.65 (4H, $CSNCH_2$), 3.17 (4H, $CONCH_2$), 1.13, 1.11 (6H, $CSNCH_2CH_3$), 1.01 (6H, $CONCH_2CH_3$)
11	5.82	4.51	5.13	4.05	3.66	4.39	4.05	1.43	1.24			3.17 (6H, $NHCH_2$), 1.06, 1.04 (9H, CH_3)
12	5.83	4.60	5.94	4.17	3.77	4.42	4.09	1.47	1.27			3.77, 3.42 (4H, $CSNCH_2$), 3.16 (2H, $CONHCH_2$), 1.20 (3H, $CONHCH_2CH_3$), 1.13, 1.07 (6H, $CSNCH_2CH_3$)
13	5.72	4.69	4.77	4.36	4.05	4.36	4.05	1.48	1.27			3.94, 3.69 (4H, $CSNCH_2$), 3.12 (2H, $COHNCH_2$), 1.22, 1.20 (6H, $CSNCH_2CH_3$), 1.04 (3H, $CONHCH_2CH_3$)
14 (*Z*)	5.84	4.52	5.16	4.13	3.79	4.83	4.35	1.45	1.26			3.50 (2H, $CSNHCH_2$), 3.19 (4H, $CONCH_2$), 1.17 (3H, $CSNHCH_2CH_3$), 1.08 (6H, $CONCH_2CH_3$)
14 (*E*)	5.84	4.52	5.16	4.13	3.79	4.83	4.35	1.45	1.26			3.33 (2H, $CSNHCH_2$), 3.19 (4H, $CONCH_2$), 1.17 (3H, $CSNHCH_2CH_3$), 1.08 (6H, $CONCH_2CH_3$)
15	5.71	4.40	4.99	3.97	3.75	3.77	3.27	1.32	1.11			3.77, 3.61 (4H, $CSNCH_2$), 3.07 (4H, $CONCH_2$), 1.04 (6H, $CONCH_2CH_3$), 0.93 (6H, C-6-$SCSNCH_2CH_3$)
16	5.83	4.64	5.87	4.19	3.98	3.98	3.47	1.48	1.26			3.92, 3.72 (4H, C-6-$SCSNCH_2$), 3.74, 3.40 (4H, C-3-$OCSNCH_2$), 1.22, 1.20 (6H, C-6-$SCSNCH_2CH_3$), 1.11, 1.09 (6H, C-3-$OCSNCH_2CH_3$)

Table 2: ^{1}H NMR Coupling Constants (in Hz) for compounds **1'** and **2 - 16**.

Compd	Coupling constances (Hz)							
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	Others
1'	3.5	4.0				4.0	10.0	$J_{o,m}$ = 8.3
2	3.9	0	3.6	8.8		7.1	14.4	
3	3.6	0	2.4	7.8	5.9	4.8	8.5	$J_{NCH_2-CH_3}$ = 7.1
4	3.8	0	2.6		5.3	4.6	8.3	$J_{NCH_2-CH_3}$ = 7.0
5	3.5	0	3.5	8.2	6.1	5.0	8.7	$J_{NCH_2-CH_3}$ = 6.9
6	3.7	0	2.7	9.5	4.8	5.9	11.8	$J_{NCH_2-CH_3}$ = 7.0
7	3.7	0	2.3	9.0	5.3	4.6	8.3	$J_{NCH_2-CH_3}$ = 7.0
8	3.6	0	3.5	8.9	3.5	5.9	11.4	$J_{NCH_2-CH_3}$ = 7.1
9	3.5	0	2.3	11.7	2.3	5.0	11.8	$J_{NCH_2-CH_3}$ = 7.0
10	3.7	0	2.6	9.3	2.7	4.9	11.9	$J_{NCH_2-CH_3}$ = 7.1
11	3.6	0	2.3					
12	3.5	0	3.7	9.0	2.2	5.0	12.0	
13	3.3	0	3.4					
14 (*Z*)	3.6	0	1.9	7.2		6.6	11.4	
14 (*E*)	3.6	0	1.9	7.2	1.7	6.6	11.4	$J_{NCH_2-CH_3}$ = 7.1
15	3.6	0	2.2	8.9		7.5	13.9	
16	3.7	0	2.7	8.7		8.1	15.3	

Step b: Selective partial acid-catalyzed deprotection of derivatives **3-5** in 1,4-dioxane-H_2O-HCl at 30 °C afforded the intermediates **6-8** in yields ranging from 70 to 88%. Neither intramolecular transcarbamoylation nor decarbamoylation was observed in acidic (during the deprotection reaction), neutral and basic (during product extraction - see experimental section) medium. Such an observation is in contrast with that found for the analogous carboxylic acid esters[16-18] or carbamoyl acid esters.[19-21] However, in the latter carbamoyl derivatives, product degradation was observed under strong basic[19-20] or strong acidic conditions[21] after 5 to 20 h.

The structures of the 3-carbamoyl ester derivatives of D-glucose **3-8** were supported by the ^{13}C, ^{1}H NMR data and elemental analyses. In comparison with that of the parent sugar, the *O*-carbamoyl ester **6** showed a downfield shift for the resonance of H-3 (ca. +0.9 ppm), H-2 (ca. +0.1 ppm), H-4 (ca. +0.2 ppm) and C-3 (ca. +3.2 ppm) along with an upfield shift of the resonance of C-2 (ca. -2.0 ppm) and C-4 (ca. -1.8 ppm). These phenomena were amplified for the H-3 and C-3 signals of the *O*-thiocarbamoyl ester

Table 3: ^{13}C NMR Chemical Shifts (δ in ppm, in $CDCl_3$) for Compounds **1'** and **2 - 13**.

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
1'	103.0	82.6	18.1	81.5	69.4	70.7	111.9		26.6	26.5	144.9 (C-ipso), 132.6 (C-para), 129.9 (C-ortho), 127.9 (C-meta)
2	104.5	86.6	57.3	80.4	69.9	40.6	111.2		26.6	26.4	196.6 (C-3-SCS), 192.6 (C-6SCS), 50.0, 47.1 (2C, C-6-SCSN CH_2), 49.7, 47.1 (2C, C-3-SCSNCH_2), 12.5, 11.5 (4C, CH_3)
3	104.8	83.5	77.0	80.0	72.6	67.2	112.0	109.1	26.6 26.6	26.1 25.1	154.3 (CO), 41.9, 41.2 (2C, NCH_2), 13.9, 13.3 (2C, CH_3)
4	104.7	83.5	79.9	82.2	72.4	67.4	112.1	109.3	27.7 26.6	26.1 25.1	185.5 (CS), 47.9, 43.3 (2C, NCH_2), 13.2, 11.7 (2C, CH_3)
5	104.5	86.7	57.1	74.0	73.9	67.4	112.1	109.4	26.7 26.5	26.3 25.2	191.9 (CS), 49.3, 46.6 (2C, NCH_2), 12.4, 11.4 (2C, CH_3)
6	104.3	82.6	76.3	78.1	68.4	63.4	110.8		26.3	25.9	153.9 (CO), 41.3, 40.8 (2C, NCH_2), 13.8, 13.2 (2C, CH_3)
7	104.8	83.2	82.0	80.3	67.5	64.2	112.4		26.6	26.2	185.8 (CS), 48.5, 43.9 (2C, NCH_2), 13.1, 11.7 (2C, CH_3)
8	104.5	85.9	58.5	78.8	70.3	64.1	112.2		26.4	26.2	192.7 (CS), 50.2, 47.4 (2C, NCH_2), 12.5, 11.4 (2C, CH_3)
9	104.7	83.2	77.1	79.1	67.0	66.6	111.8		26.5	26.1	156.3 (C-6-OCO), 155.2 (C-3-OCO), 42.1, 41.5 (4C, NCH_2), 13.8, 12.1 (4C, CH_3)
10	104.7	83.3	78.9	81.9	67.3	66.9	112.0		26.5	26.2	185.7 (CS), 156.6 (CO), 48.2, 43.6 (2C, CSNCH_2), 41.8, 41.4 (2C, CONCH_2), 13.9, 13.1 (2C, CONCH$_2CH_3$), 13.1, 11.7 (2C, CSNCH$_2CH_3$)
11	104.8	83.2	77.2	79.4	66.9	66.3	112.2		26.5	26.3	155.6 (C-6-OCO), 155.4 (C-3-OCO), 42.3, 41.6 (2C, C-3-OCONCH_2), 35.8 (C-6-OCONHCH_2), 15.0 (1C, C-6-OCO NHCH$_2CH_3$), 13.8, 13.2 (2C, C-3-OCONCH$_2CH_3$)
12	104.7	83.4	82.0	79.2	67.0	66.5	112.3		26.6	26.2	185.8 (CS), 156.6 (CO), 48.3, 43.7 (2C, CSNCH_2), 35.9 (1C, CONHCH_2), 15.0 (1C, CONHCH$_2CH_3$), 13.2, 11.7 (2C, CSNCH$_2CH_3$)
13	104.5	86.3	58.3	78.2	69.2	66.6	112.2		26.5	26.3	192.6 (CS), 156.7 (CO), 50.0, 47.2 (2C, CSNCH_2), 35.9, 35.1 (2C, CONHCH_2), 15.7, 15.0 (2C, CONHCH$_2CH_3$), 12.5, 11.3 (2C, CSNCH$_2CH_3$)

Table 4: ^{13}C NMR Chemical Shifts (δ in ppm, in $CDCl_3$) for Compounds **14 - 19**.

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
14 (*Z*)	104.8	83.2	77.1	79.6	71.3	66.7	112.2	26.6	26.2	190.0 (CS), 155.5 (CO), 42.4, 41.7 (2C, $CONCH_2$), 40.1 (1C, $CSNHCH_2$), 13.8, 13.2 (2C, $CONCH_2CH_3$), 13.6 (1C, $CSNHCH_2CH_3$)
14 (*E*)	104.8	83.2	77.1	79.6	71.6	66.5	112.2	26.6	26.2	190.0 (CS), 155.5 (CO), 42.4, 41.7 (2C, $CONCH_2$), 38.1 (1C, $CSNCH_2$), 14.2 (1C, $CSNCH_2CH_3$), 13.8, 13.2 (2C, $CONCH_2CH_3$),
15	104.7	83.2	76.8	81.7	67.3	40.9	111.9	26.6	26.1	195.9 (CS), 155.0 (CO), 49.6, 46.8 (2C, $CSNCH_2$), 42.2, 41.5 (2C, $CONCH_2$), 13.8, 13.1 (2C, $CONCH_2CH_3$), 12.3, 11.3 (2C, $CSNCH_2CH_3$)
16	104.7	83.5	81.5	81.9	67.7	40.6	112.2	26.7	26.3	196.4 (SCS), 185.7 (OCS), 49.9, 47.0 (2C, $SCSNCH_2$), 48.1, 43.7 (2C, $OCSNCH_2$), 13.3, 11.7 (2C, $OCSNCH_2CH_3$), 12.4, 11.5 (2C, $SCSNCH_2CH_3$)
17[a] (α)	91.7	71.2	57.3	70.7	70.9	40.5				195.9 (C-6-SCS), 194.3 (C-3-SCS), 49.3, 46.9 (2C, C-6-$SCSNCH_2$), 48.9, 46.4 (2C, C-3-$SCSNCH_2$), 12.3, 11.4 (4C, CH_3)
17[a] (β)	98.4	72.3	60.8	71.8	76.4	40.5				195.2 (C-6-SCS), 194.2 (C-3-SCS), 49.3, 46.9 (2C, C-6-$SCSNCH_2$), 48.9, 46.4 (2C, C-3-$SCSNCH_2$), 12.3, 11.4 (4C, CH_3)
18[a] (α)	92.1	70.6	76.1	68.7	69.5	63.9				155.6 (C-6-OCO), 154.9 (C-3-OCO), 40.9 (4C, NCH_2), 13.7 (4C, CH_3)
18[a] (β)	96.7	73.0	78.4	68.7	73.6	64.0				155.3 (2C, CO), 40.9 (4C, NCH_2), 13.7 (4C, CH_3)
19[a] (α)	92.2	71.9	76.0	69.4	71.7	40.3				194.3 (CS), 155.3 (CO), 48.8, 46.4 (2C, $CSNCH_2$), 41.0 (2C, $CONCH_2$), 13.6 (2C, $CONCH_2CH_3$), 12.3, 11.3 (2C, $CSNCH_2CH_3$)
19[a] (β)	96.8	73.1	78.3	70.6	73.6	41.3				194.3 (CS), 155.6 (CO), 48.8, 46.4 (2C, $CSNCH_2$), 41.0 (2C, $CONCH_2$), 13.6 (2C, $CONCH_2CH_3$), 12.3, 11.3 (2C, $CSNCH_2CH_3$)

a. Spectra were recorded in $(CD_3)_2SO$.

7 having a thiocarbonyl group such as H-3 (ca. +2.0 ppm), H-2 (ca. +0.2 ppm), H-4 (ca. +0.3 ppm), C-3 (ca. +8.9 ppm), C-2 (ca. -1.4 ppm) and C-4 (ca. +0.4 ppm)). The *S*-thiocarbamoyl ester **8** showed a downfield shift for the resonance of H-3 (ca. +0.7 ppm), H-2 (ca. +0.3 ppm), H-4 (ca. +0.5 ppm) and C-2 (ca. +1.3 ppm) along with an upfield shift of the resonance of C-3 (ca. -14.6 ppm) and C-4 (ca. -1.1 ppm). The proton and carbon signals of 3-carbamoyl ester derivatives of D-glucose **3-5** were similar to those described above.

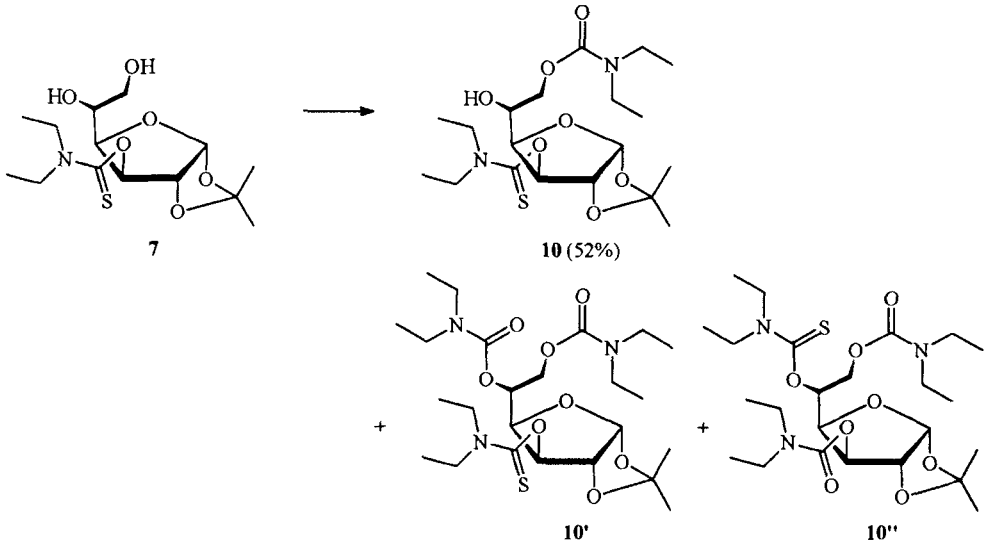
Step c: Regioselective *N,N*-diethylcarbamoylation at C-6 of compounds **6** and **7** with *N,N*-diethylcarbamoyl chloride (1.0 equiv) in the presence of finely powdered KOH (2.0 equiv) in toluene at 0 °C gave the bis-3,6-*O*-(*N,N*-diethylcarbamoyl) esters **9** (2.6 h in 69% yield) and the 6-*O*-(*N,N*-diethylcarbamoyl)-3-*O*-(*N,N*-diethylthiocarbamoyl) esters **10** (2.3 h in 52% yield) respectively. Each of these reactions gave two by-products in small amounts due to competitive reactions during carbamoylation of compounds **6** and **7** (Scheme 3) respectively. Thus the carbamoylation of **7** gave:

(i) bis-5,6-*O*-(*N,N*-diethylcarbamoyl)-3-*O*-(*N,N*-diethylthiocarbamoyl)-1,2-*O*-isopropylidene α-D-glucofuranose (**10'**) by carbamoylation at C-5 and C-6 sites;

(ii) bis-3,6-*O*-(*N,N*-diethylcarbamoyl)-5-*O*-(*N,N*-diethylthiocarbamoyl)-1,2-*O*-isopropylidene-α-D-glucofuranose (**10''**) by internal transthiocarbamoylation from C-3 to C-5 position followed by reaction of the liberated C-3 alcoholate with *N,N*-diethylcarbamoyl chloride. *N,N*-diethylcarbamoylation of thiocarbamate derivative **7** allowed us to verify the transesterification phenomenon since the diester **10** gave the triester **10''**, in basic media, by migration of the thioamide group from C-3 to C-5 position through a cyclic intermediate.

Similary, the by-products obtained from the carbamoylation of **6** were both tris-3,5,6-*O*-(*N,N*-diethylcarbamoyl)-1,2-*O*-isopropylidene-α-D-glucofuranose (**9'**) and bis-5,6-*O*-(*N,N*-diethylcarbamoyl)-1,2-*O*-isopropylidene-α-D-glucofuranose (**9''**).

Regiospecific *N*-ethylcarbamoylation at C-6 of compounds **6-8** with ethyl isocyanate and ethyl isothiocyanate (2.0 equiv) in pyridine at 40 °C gave the 6-*O*-(*N*-ethyl carbamate) derivatives **11-13** (48-72 h in 91-98% yield) and the 6-*O*-(*N*-ethyl thiocarbamate) derivatives **14** (96 h in 98% yield) respectively. We did not detect any other product in the reaction mixture indicating that neither C-5 carbamoylation, nor transcarbamoylation from C-3 to C-5 took place. It is important to note the feature



$(C_2H_5)_2NCOCl$, KOH, toluene, 0 °C, 2.3 h.

Scheme 3

distinguishing the *N*-alkyl carbamate and the *N*-alkyl thiocarbamate.[22] It is known that there is a high barrier to rotation around the N-CS bond.[23] We also observed this phenomenon with the *N*-ethylthiocarbamoyl ester **14** using NMR spectroscopy but not with the *N*-ethylcarbamoyl ester **11** due to the free rotation of the carbamoyl bond. The methylene proton signals assigned to NCH_2 of the thiocarbamoyl group are indicative of the *Z* and *E* conformations[24] for compound **14** because the thiocarbonyl group anisotropy caused deshielding of CH_2 in the *Z* conformer (ca. +0.17 ppm).

Regiospecific *N,N*-diethyldithiocarbamoylation at C-6 of compounds **6-8** was performed by C-6 tosylation[25] followed by substitution with lithium *N,N*-diethyl dithiocarbamate in acetone at 56 °C, to give the 6-*S*-(*N,N*-diethyl dithiocarbamate) derivatives **15**, **16** and **2** (1-4.5 h in 72-89% yield starting from the tosylate precursor). It is interesting to observe that compound **2** is obtained in 28% overall yield from compound **1** using the pathway shown in Scheme 2 instead of 22% as outlined in Scheme 1 which involves the intermediate . The route shown in Scheme 2 has the advantage that it permits convenient access to a large range of products having identical or different carbamoyl

groups at the C-3 and C-6 positions whereas the route outlined in Scheme 1 led only to compounds with the same carbamoyl group in each position.

Step d: The biscarbamate derivatives **2**, **9** and **15** were each deprotected to complete the product range and to extend the hydrophilic-lipophilic balance. This step was performed using 1,4-dioxane-H_2O-HCl at 60 °C (instead of 30 °C which was used to prepare partially deprotected compounds **3-5**) to give **17-19** respectively (2 h in 50-70% yield).

Antifungal properties. Of the bis(carbamoyl esters) tested using a solid medium (Czapek Yeast Agar, glycine, agar[26]) and a Fayret liquid medium (glucose, ammonium nitrate[27]), antifungal activities were observed for compounds **2** and **17**; each had the same bis(*N,N*-diethyldithiocarbamoyl group) at C-3 and C-6 but differed by having: (i) one or three hydroxyl groups free (corresponding to the presence or absence of an isopropylidene group respectively); (ii) furanosyl or pyranosyl forms respectively. Compound **2** inhibited sporulation of *Botrytis cinerea* (no-operating conidiophore formation after 4 days at 100 ppm) and mycellium growth of *Fusarium oxysporum f.sp. lini* (mycellium growth inhibition: 17% after 4 days at 200 ppm). **17** inhibited mycellium growth of *Botrytis cinerea* (mycellium growth inhibition: 50% after 4 days at 200 ppm) and *Fusarium oxysporum f.sp. lini* (mycellium growth inhibition: 18% after 4 days at 200 ppm). These results showed that the type of saccharide moiety was important for biological activity since the bis(dithiocarbamoyl esters) **2** and **17** had selective antifungal activities at different stages of the fungal growth.

EXPERIMENTAL

General Procedure. 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 (Brüker 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). 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (**1**), *N,N*-diethylcarbamoyl chloride, ethyl isocyanate, ethyl isothiocyanate, bases and solvents were supplied by JANSSEN or ALDRICH.

***N,N*-Diethyldithiocarbamic acid lithium salt** was synthesized in accordance with the method described by Postel.[15]

3-Deoxy-3-iodo-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose was synthesized in accordance with the method described by Garegg.[14]

3-Deoxy-3-iodo-1,2-*O*-isopropylidene-6-*O*-tosyl-α-D-allofuranose (1'). 3-Deoxy-3-iodo-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (7.0 g, 18.9 mmol) was reacted with a 0.6M HCl in water-dioxane (7:93, 65 mL) at 30 °C during 30 min. After addition of sodium hydrogen carbonate (pH 7), the mixture was stirred for 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 (1:1) to give 4.0 g (64%) of 3-deoxy-3-iodo-1,2-*O*-isopropylidene-α-D-allofuranose, mp 110-111 °C; $[\alpha]_D^{22}$ +113° (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.76 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 4.57 (t, 1H, $J_{2,3}$ = 4.2, H-2), 4.25 (dd, 1H, $J_{4,5}$ = 2.9 Hz, H-4), 4.00 (m, 1H, $J_{5,6}$ = 7.2 Hz, H-5), 3.88 (dd, 1H, $J_{3,4}$ = 10.2 Hz, H-3), 3.83 (dd, 1H, $J_{6,6'}$ = 11.5 Hz, H-6), 3.68 (dd, 1H, $J_{5,6'}$ = 3.9 Hz, H-6'), 1.45, 1.27 (s, 6H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ 111.8 ($C(CH_3)_2$), 103.0 (C-1), 83.5 (C-2), 81.5 (C-4), 71.5 (C-5), 63.4 (C-6), 26.5 (2C, $C(CH_3)_2$), 18.7 (C-3).

p-Toluenesulphonyl chloride (4.0 g, 21.2 mmol) dissolved in toluene (27 mL) was slowly added to a stirred pyridine (27 mL) solution of 3-deoxy-3-iodo-1,2-*O*-isopropylidene-α-D-allofuranose (7.0 g, 21.2 mmol) at 0 °C. After 48 h at 4 °C, crushed ice and aqueous-HCl (9:1) (50 mL) were added to the mixture and two phases separated. The aqueous phase was extracted with toluene (2x25 mL); the organic phases were pooled, dried (Na_2SO_4) and concentrated. The crude product was purified on a silica gel column eluted with hexane-acetone (4:1) to give 8.6 g (84%) of **1'**. $[\alpha]_D^{22}$ +233° (*c* 1.2, $CHCl_3$).

Anal. Calcd for $C_{16}H_{21}O_7SI$ (484.31): C, 39.68; H, 4.37, S, 6.62. Found: C, 39.42; H, 4.54, S, 7.01.

3,6-Dideoxy-bis-3,6-*S*-(*N,N*-diethyldithiocarbamoyl)-1,2-*O*-isopropylidene-α-D-glucofuranose (2).

Method a: *N,N*-Diethyldithiocarbamic acid lithium salt (1.9 g, 12.4 mmol) was added dropwise to a stirred solution of **1'** (1.5 g, 3.1 mmol) in HMPA-toluene (1:1) (5 mL). Upon completion of the addition, the reaction mixture was stirred at 110 °C for 24 h. The mixture was filtered and the solvent removed by distillation under reduced pressure to yield a viscous oil. This oily residue was treated with hexane-diethyl ether (1:1) and 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 0.9 g (60%) of **2**. $[\alpha]_D^{22}$ +48° (*c* 1.1, $CHCl_3$).

Anal. Calcd for $C_{19}H_{34}O_4S_4N_2$ (482.75): C, 47.27; H, 7.10; S, 26.57; N, 5.80. Found: C, 47.21; H, 7.02; S, 27.02; N, 5.82.

Method b: *p*-Toluenesulphonyl chloride (3.8 g, 19.9 mmol) dissolved in toluene (25 mL) was slowly added to a stirred pyridine (25 mL) solution of **8** (7.0 g, 19.9 mmol) at 0 °C. After 48 h at 4 °C, crushed ice and aqueous-HCl (9:1) (50 mL) were added to the mixture and two phases separated. The aqueous phase was extracted with toluene (2x25 mL); the organic phases were pooled, dried (Na_2SO_4) and concentrated. The crude product was purified on a silica gel column eluted with hexane-diethyl ether (4:1) to give 8.8 g (87% yield) of 3-deoxy-3-*S*-(*N,N*-diethyldithiocarbamoyl)-1,2-*O*-isopropylidene-6-*O*-tosyl-α-D-glucofuranose (**8'**). $[\alpha]_D^{22}$ +76° (*c* 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.75 (d, 2H, $J_{o,m}$ = 8.3 Hz, H-ortho), 7.27 (d, 2H, H-meta), 5.69 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 4.84 (d, 1H, $J_{3,4}$ = 3.4 Hz, H-3), 4.71 (d, 1H, $J_{2,3}$ = 0, H-2), 4.27 (dd, 2H, H-6, H-6'), 4.00 (dd, 1H, $J_{4,5}$ = 11.7 Hz, H-4), 3.92 (m, 1H, H-5), 4.00, 3.70 (q, 4H, NCH_2), 2.38 (s, 3H, CH_3), 1.46, 1.25 (s, 6H, $C(CH_3)_2$), 1.25, 1.22 (t, 6H, J = 7.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 192.4 (CS), 144.6 (C-ipso), 132.9 (C-para), 129.7 (C-ortho), 128.0 (C-meta), 112.2 ($C(CH_3)_2$), 104.5 (C-1), 85.9 (C-2), 78.1 (C-4), 71.8 (C-5), 68.7 (C-6), 58.5 (C-3), 50.4, 47.4 (2C, NCH_2), 26.4, 26.2 (2C, $C(CH_3)_2$), 21.5 (CH_3), 12.5, 11.4 (2C, NCH_2CH_3). *N,N*-Diethyldithiocarbamic acid lithium salt (2.3 g, 14.8 mmol) and **8'** (5.0 g, 9.9 mmol) in acetone (40 mL) was stirred at 56 °C for 4.5 h. The mixture was filtered and acetone was removed by distillation under reduced pressure to yield a viscous oil. This oily residue was treated with hexane-diethyl ether (1:1) and 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 3.4 g (72%) of **2**.

3-*O*-(*N,N*-Diethylcarbamoyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (3). *N,N*-Diethylcarbamoyl chloride (3.1 g, 22.9 mmol) was added dropwise to a stirred solution of **1** (5.0 g, 19.2 mmol) and KOH (2.2 g, 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 (9:1) to give 5.6 g (81%) of **3**. $[\alpha]_D^{22}$ -38° (*c* 1.5, $CHCl_3$).

Anal. Calcd for $C_{17}H_{29}O_7N$ (359.42): C, 56.81; H, 8.13; N, 3.90. Found: C, 56.86; H, 8.15; N, 4.11.

3-*O*-(*N,N*-Diethylthiocarbamoyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (4). To a stirred solution of thiophosgene (2.9 g, 25.2 mmol) in toluene (27 mL) at 8 °C was added diethylamine (3.7 g, 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 **1** (5.0 g, 19.2 mmol) and potassium *t*-butoxide (2.6 g, 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 6.2 (85%) of **4**, mp 53-54 °C; $[\alpha]_D^{22}$ -69° (*c* 1.6, $CHCl_3$).

Anal. Calcd for $C_{17}H_{29}O_6SN$ (375.49): C, 54.38; H, 7.78; S, 8.54; N, 3.73. Found: C, 54.10; H, 7.71; S, 8.35; N, 3.46.

3-Deoxy-3-*S*-(*N,N*-diethyldithiocarbamoyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (5). A solution of 3-deoxy-3-iodo-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (10.0 g, 27.0 mmol) and *N,N*-diethyldithiocarbamic acid lithium salt (6.3 g, 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 **5**, mp 83-84 °C; $[\alpha]_D^{22}$ -44° (*c* 1.5, $CHCl_3$).

Anal. Calcd for $C_{17}H_{29}O_5S_2N$ (391.55): C, 52.15; H, 7.46; S, 16.38; N, 3.58. Found: C, 52.21; H, 7.55; S, 16.60; N, 3.62.

3-*O*-(*N,N*-Diethylcarbamoyl)-1,2-*O*-isopropylidene-α-D-glucofuranose (6). **3** (7.0 g, 19.5 mmol) was reacted with a 0.6M HCl in water-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 (1:1) to give 4.3 g (70%) of **6**. $[\alpha]_D^{22}$ +64° (*c* 1.4, $CHCl_3$).

Anal. Calcd for $C_{14}H_{25}O_7N$ (319.35): C, 52.65; H, 7.89; N, 4.39. Found: C, 52.52; H, 8.03; N, 4.17.

3-*O*-(*N,N*-Diethylthiocarbamoyl)-1,2-*O*-isopropylidene-α-D-glucofuranose (7). Likewise, **4** (7.0 g, 18.7 mmol) gave, after 30 min, 5.5 g (88%) of **7**, mp 84-85 °C; $[\alpha]_D^{22}$ +64° (*c* 1.4, $CHCl_3$).

Anal. Calcd for $C_{14}H_{25}O_6SN$ (335.42): C, 50.13; H, 7.51; S, 9.56; N, 4.18. Found: C, 50.20; H, 7.63; S, 10.05; N, 4.31.

3-Deoxy-3-*S*-(*N,N*-diethyldithiocarbamoyl)-1,2-*O*-isopropylidene-α-D-glucofuranose (8). Likewise, **5** (10.0 g, 25.6 mmol) gave, after 30 min, 6.8 g (75%) of **8**, mp 78-80 °C; $[\alpha]_D^{22}$ +91° (*c* 1.2, $CHCl_3$).

Anal. Calcd for $C_{14}H_{25}O_5S_2N$ (351.49): C, 47.84; H, 7.17; S, 18.25; N, 3.98. Found: C, 47.76; H, 7.03; S, 18.95; N, 4.02.

Bis-3,6-*O*-(*N,N*-diethylcarbamoyl)-1,2-*O*-isopropylidene-α-D-glucofuranose (9). A solution of *N,N*-diethylcarbamoyl chloride (0.8 g, 6.3 mmol) in toluene (4 mL) was added dropwise to a stirred solution of **6** (2.0 g, 6.3 mmol) and KOH (0.7 g, 12.5 mmol) in toluene (20 mL) at 0 °C. Stirring was continued at 0 °C until HPLC monitoring indicated that maximum conversion was achieved (2.6 h), whereupon a saturated aqueous solution of ammonium chloride 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-diethyl ether (4:1) to give 0.2 g of a mixture containing tris-3,5,6-*O*-(*N,N*-diethylcarbamoyl)-1,2-

O-isopropylidene-α-D-glucofuranose (**9'**) (95% estimated by ^{1}H and ^{13}C NMR integration). ^{1}H NMR ($CDCl_3$) δ 5.69 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 5.00 (d, 1H, $J_{3,4}$ = 3.0 Hz, H-3), 4.91 (dq, 1H, $J_{5,6}$ = 2.2 Hz, H-5), 4.37 (dd, 1H, $J_{5,6'}$ = 4.1 Hz, H-6), 4.34 (d, 1H, $J_{2,3}$ = 0, H-2), 4.30 (dd, 1H, $J_{4,5}$ = 9.4 Hz, H-4), 3.97 (dd, 1H, $J_{6,6'}$ = 12.1 Hz, H-6'), 3.05 (m, 12H, NCH_2), 1.30, 1.10 (s, 6H, $C(CH_3)_2$), 0.89, 0.86 (t, 18H, J = 7.2 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 155.2 (C-6-O*C*O), 153.8 (2C, C-3-O*C*O, C-5-O*C*O), 111.9 (*C*$(CH_3)_2$), 104.8 (C-1), 83.3 (C-2), 76.8 (C-4), 76.0 (C-3), 68.9 (C-5), 64.0 (C-6), 41.8, 41.1 (6C, NCH_2), 26.6, 26.0 (2C, C(*C*$H_3)_2$), 13.8, 13.2 (6C, CH_3).

Further elution provided 0.1 g of a mixture containing bis-5,6-*O*-(*N,N*-diethylcarbamoyl)-1,2-*O*-isopropylidene-α-D-glucofuranose (**9''**) (94% estimated by ^{1}H and ^{13}C NMR integration). ^{1}H NMR ($CDCl_3$) δ 5.81 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 4.92 (m, 1H, H-5), 4.45 (dd, 1H, $J_{5,6}$ = 2.3 Hz, H-6), 4.44 (d, 1H, $J_{2,3}$ = 0, H-2), 4.26 (dd, 1H, $J_{5,6'}$ = 5.0 Hz, $J_{6,6'}$ = 11.8 Hz, H-6'), 4.01 (dd, 1H, $J_{4,5}$ = 11.7 Hz, H-4), 3.96 (d, 1H, $J_{3,4}$ = 2.3 Hz, H-3), 3.16 (m, 8H, NCH_2), 1.38, 1.21 (s, 6H, $C(CH_3)_2$), 1.01, 1.00 (t, 18H, J = 7.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 156.1 (C-6-O*C*O), 155.3 (C-5-O*C*O), 111.5 (*C*$(CH_3)_2$), 105.1 (C-1), 84.4 (C-2), 79.3 (C-4), 73.6 (C-3), 70.2 (C-5), 64.4 (C-6), 42.2, 41.5 (4C, NCH_2), 26.7, 26.0 (2C, C(*C*$H_3)_2$), 13.7, 13.1 (4C, CH_3). Further elution provided 1.8 g (69%) of **9**, mp 50-52 °C, $[\alpha]_D^{22}$ +15° (*c* 1.1, $CHCl_3$).

Anal. Calcd for $C_{19}H_{34}O_8N_2$ (418.49): C, 54.53; H, 8.19; N, 6.69. Found: C, 54.71; H, 8.32; N, 6.57.

Further elution provided 0.5 g of the initial product **6**.

6-*O*-(*N,N*-Diethylcarbamoyl)-3-*O*-(*N,N*-diethylthiocarbamoyl)-1,2-*O*-isopropylidene-α-D-glucofuranose (10). Likewise, **7** (5.0 g, 14.9 mmol) and *N,N*-diethylcarbamoyl chloride (2.0 g, 14.9 mmol) gave, after 2.3 h, 0.4 g of a mixture containing bis-5,6-*O*-(*N,N*-diethylcarbamoyl)-3-*O*-(*N,N*-diethylthiocarbamoyl)-1,2-*O*-isopropylidene-α-D-glucofuranose (**10'**) (96% estimated by ^{1}H and ^{13}C NMR integration). ^{1}H NMR ($CDCl_3$) δ 5.76 (d, 1H, $J_{3,4}$ = 2.8 Hz, H-3), 5.73 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 4.97 (m, 1H, $J_{5,6}$ = 2.2 Hz, H-5), 4.48 (d, 1H, $J_{2,3}$ = 0, H-2), 4.42 (dd, 1H, $J_{5,6'}$ = 4.2 Hz, H-6), 4.41 (dd, 1H, $J_{4,5}$ = 9.3 Hz, H-4), 4.03 (dd, 1H, $J_{6,6'}$ = 12.1 Hz, H-6'), 3.75, 3.65, 3.46, 3.00 (m, 4H, C-3-OCSNCH_2), 3.10 (m, 8H, C-5-OCONCH_2, C-6-OCONCH_2), 1.37, 1.16

(s, 6H, $C(CH_3)_2$), 1.05, 1.00 (t, 6H, J = 7.2 Hz, C-3-OCSNCH$_2$C*H*$_3$), 0.95 (t, 12H, J = 7.2 Hz, C-5-OCONCH$_2$C*H*$_3$, C-6-OCONCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 185.0 (CS), 155.2 (C-6-O*C*O), 153.7 (C-5-O*C*O), 112.1 (*C*$(CH_3)_2$), 104.9 (C-1), 83.3 (C-2), 81.2 (C-4), 76.6 (C-3), 68.8 (C-5), 64.0 (C-6), 47.9, 43.8 (2C, C-3-OCSN*C*H$_2$), 43.8, 41.3 (4C, C-5-OCON*C*H$_2$, C-6-OCON*C*H$_2$), 26.6, 26.1 (2C, (C(*C*H$_3$)$_2$), 13.9, 13.1 (4C, C-5-OCONCH$_2$*C*H$_3$, C-6-OCONCH$_2$*C*H$_3$), 13.1, 11.6 (2C, C-3-OCSNCH$_2$*C*H$_3$).

Further elution provided 0.2 g of a mixture containing bis-3,6-*O*-(*N,N*-diethylcarbamoyl)-5-*O*-(*N,N*-diethylthiocarbamoyl)-1,2-*O*-isopropylidene-α-D-glucofuranose (**10''**) (95% estimated by ^{1}H and ^{13}C NMR integration). ^{1}H NMR ($CDCl_3$) δ 5.84 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 5.20 (m, 1H, H-5), 5.16 (d, 1H, $J_{3,4}$ = 2.9 Hz, H-3), 4.87 (dd, 1H, $J_{4,5}$ = 11.9 Hz, H-4), 4.49 (d, 1H, $J_{2,3}$ = 0, H-2), 4.46 (dd, 1H, $J_{5,6}$ = 2.2 Hz, $J_{6,6'}$ = 12.1 Hz, H-6), 4.42 (dd, 1H, $J_{5,6'}$ = 4.2 Hz, H-6'), 3.74, 3.42, 3.10 (m, 4H, C-5-OCSNCH$_2$), 3.18 (m, 8H, C-3-OCONCH$_2$, C-6-OCONCH$_2$), 1.45, 1.25 (s, 6H, $C(CH_3)_2$), 1.03 (m, 18H, CH_3); ^{13}C NMR ($CDCl_3$) δ 185.0 (CS), 156.0 (2C, CO), 112.0 (*C*$(CH_3)_2$), 107.7 (C-1), 83.5 (C-2), 77.3 (C-4), 76.1 (C-3), 70.4 (C-5), 68.8 (C-6), 47.8, 43.7 (2C, C-5-OCSN*C*H$_2$), 2x42.2, 42.0, 41.3 (4C, C-3-OCON*C*H$_2$, C-6-OCON*C*H$_2$), 26.7, 26.1 (2C, C(*C*H$_3$)$_2$), 13.9, 13.2 (4C, C-3-OCONCH$_2$*C*H$_3$, C-6-OCONCH$_2$*C*H$_3$), 13.2, 11.7 (2C, C-5-OCSNCH$_2$*C*H$_3$). Further elution provided 3.4 g (52%) of **10**. $[\alpha]_D^{22}$ +53° (*c* 1.2, $CHCl_3$).

Anal. Calcd for $C_{19}H_{34}O_7SN_2$ (434.55): C, 52.52; H, 7.89; S, 7.38; N, 6.45. Found: C, 52.75; H, 7.81; S, 7.59; N, 6.54.

Further elution provided 1.5 g of the initial product **7**.

3-*O*-(*N,N*-Diethylcarbamoyl)-6-*O*-(*N*-ethylcarbamoyl)-1,2-*O*-isopropylidene-α-D-glucofuranose (11). A solution of **6** (2.0 g, 6.3 mmol) and ethyl isocyanate (0.9 g, 12.5 mmol) in pyridine (20 mL) was stirred at 40 °C for 48 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 2.4 g (98%) of **11**. $[\alpha]_D^{22}$ +36° (*c* 1.1, $CHCl_3$).

Anal. Calcd for $C_{17}H_{30}O_8N_2$ (390.43): C, 52.30; H, 7.74; N, 7.17. Found: C, 52.00; H, 7.52; N, 7.13.

3-*O*-(*N,N*-Diethylthiocarbamoyl)-6-*O*-(*N*-ethylcarbamoyl)-1,2-*O*-isopropylidene-α-D-glucofuranose (12). Likewise, **7** (1.0 g, 3.0 mmol) and ethyl isocyanate (0.4 g, 6.0 mmol) gave, after 72 h, 1.1 g (91%) of **12**. $[\alpha]_D^{22}$ +64° (*c* 1.5, $CHCl_3$).

Anal. Calcd for $C_{17}H_{30}O_7SN_2$ (406.50): C, 50.23; H, 7.44; S, 7.89; N, 6.89. Found: C, 50.35; H, 7.51; S, 8.11; N, 6.81.

3-Deoxy-3-*S*-(*N,N*-diethyldithiocarbamoyl)-6-*O*-(*N*-ethylcarbamoyl)-1,2-*O*-isopropylidene-α-D-glucofuranose (13). Likewise, **8** (2.0 g, 5.7 mmol) and ethyl isocyanate (0.4 g, 6.0 mmol) gave, after 72 h, 2.3 g (94%) of **13**. $[\alpha]_D^{22}$ +64° (*c* 1.1, $CHCl_3$).

Anal. Calcd for $C_{17}H_{30}O_6S_2N_2$ (422.57): C, 48.32; H, 7.16; S, 15.18; N, 6.63. Found: C, 48.51; H, 7.25; S, 15.35; N, 6.58.

3-*O*-(*N,N*-Diethylcarbamoyl)-6-*O*-(*N*-ethylthiocarbamoyl)-1,2-*O*-isopropylidene-α-D-glucofuranose (14). Likewise, **6** (2.0 g, 6.3 mmol) and ethyl isothiocyanate (1.1 g, 12.5 mmol) in pyridine (5 mL) gave, after 96 h, 2.5 g (98%) of **14**. $[\alpha]_D^{22}$ +45° (*c* 1.2, $CHCl_3$).

Anal. Calcd for $C_{17}H_{30}O_7SN_2$ (406.50): C, 50.23; H, 7.44; S, 7.89; N, 6.89. Found: C, 50.07; H, 7.53; S, 7.91; N, 6.73.

6-Deoxy-3-*O*-(*N,N*-diethylcarbamoyl)-6-*S*-(*N,N*-diethyldithiocarbamoyl)-1,2-*O*-isopropylidene-α-D-glucofuranose (15). The two-step procedure for the preparation of **2** (*method b*) was applied. In the first step (*method b*), **6** (5.0 g, 15.7 mmol) gave 5.9 g (80%) of 3-*O*-(*N,N*-diethylcarbamoyl)-1,2-*O*-isopropylidene-6-*O*-tosyl-α-D-glucofuranose (**6'**). $[\alpha]_D^{22}$ +41° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.76 (d, 2H, $J_{o,m}$ = 8.2 Hz, H-ortho), 7.27 (d, 2H, H-meta), 5.80 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 5.10 (d, 1H, $J_{3,4}$ = 2.1 Hz, H-3), 4.52 (d, 1H, $J_{2,3}$ = 0, H-2), 4.31 (dd, 1H, $J_{5,6'}$ = 6.8 Hz, H-6), 4.00 (dd, 1H, $J_{4,5}$ = 9.6 Hz, H-4), 3.97 (dd, 1H, $J_{6,6'}$ = 10.2 Hz, H-6'), 3.69 (m, 1H, $J_{5,6}$ = 1.7 Hz, H-5), 3.32 (m, 2H, NCH_2), 3.19 (q, 2H, NCH_2), 2.38 (s, 3H, CH_3), 1.42, 1.25 (s, 6H, $C(CH_3)_2$), 1.08, 1.06 (t, 6H, J = 7.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 153.9 (CO), 144.5 (C-ipso), 129.7 (2C, C-ortho, C-para), 128.0 (C-meta), 112.4 ($C(CH_3)_2$), 104.8 (C-1), 83.1 (C-2), 79.2 (C-4), 77.1 (C-3), 71.6 (C-6), 66.3 (C-5), 42.4, 41.7 (2C, NCH_2), 26.6, 26.2 (2C, $C(CH_3)_2$), 21.5 (CH_3), 13.8, 13.2 (2C, NCH_2CH_3). In the second step, **6'** (2.0 g, 4.22 mmol) gave, after 1 h, 1.7 g (89%) of **15**. $[\alpha]_D^{22}$ +28° (*c* 1.2, $CHCl_3$).

Anal. Calcd for $C_{19}H_{34}O_6S_2N_2$ (450.62): C, 50.64; H, 7.60; S, 14.23; N, 6.22. Found: C, 50.60; H, 7.65; S, 14.26; N, 6.28.

6-Deoxy-3-*O*-(*N,N*-diethylthiocarbamoyl)-6-*S*-(*N,N*-diethyldithiocarbamoyl)-1,2-*O*-isopropylidene-α-D-glucofuranose (16). Likewise, in the first step, **7** (7.0 g, 20.9 mmol) gave 6.9 g (67%) of 3-*O*-(*N,N*-diethylthiocarbamoyl)-1,2-*O*-isopropylidene-6-*O*-tosyl-α-D-glucofuranose (**7'**). $[\alpha]_D^{22}$ -35° (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.67 (d, 2H, $J_{o,m}$ = 8.3 Hz, H-ortho), 7.20 (d, 2H, H-meta), 5.72 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 4.80 (d, 1H, $J_{3,4}$ = 2.3 Hz, H-3), 4.71 (dd, 1H, $J_{5,6'}$ = 2.3 Hz, H-6), 4.47 (d, 1H, $J_{2,3}$ = 0, H-2), 4.29 (dd, 1H, $J_{6,6'}$ = 11.8 Hz, H-6'), 4.02 (dd, 1H, $J_{4,5}$ = 11.7 Hz, H-4), 3.86 (m, 1H, $J_{5,6}$ = 2.3 Hz, H-5), 3.61, 3.31 (q, 4H, NCH_2), 2.27 (s, 3H, CH_3), 1.26, 1.09 (s, 6H, $C(CH_3)_2$), 1.01, 0.99 (t, 6H, J = 7.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 190.6 (CS), 145.4 (C-ipso), 132.4 (C-para), 129.9 (C-ortho), 127.9 (C-meta), 112.2 ($C(CH_3)_2$), 104.8 (C-1), 82.6 (C-2), 81.8 (C-3), 78.5 (C-4), 71.6 (C-6), 66.8 (C-5), 47.8, 43.4 (2C, NCH_2), 26.3, 26.0 (2C, $C(CH_3)_2$), 21.5 (CH_3), 13.2, 11.7 (2C, NCH_2CH_3). In the second step, **7'** (5.0 g, 10.2 mmol) gave 3.4 g (72%) of **16**. $[\alpha]_D^{22}$ +39° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{19}H_{34}O_5S_3N_2$ (466.69): C, 48.90; H, 7.34; S, 20.61; N, 6.00. Found: C, 49.20; H, 7.42; S, 20.45; N, 6.11.

3,6-Dideoxy-bis-3,6-*S*-(*N,N*-diethyldithiocarbamoyl)-D-glucopyranose (17). The procedure described for the preparation of **6** was applied to **2** (2.0 g, 4.1 mmol) at 60 °C for 2 h to give 0.9 g (50%) of **17**. $[\alpha]_D^{22}$ -38° (*c* 1.5, CH_3OH).

Anal. Calcd for $C_{16}H_{30}O_4S_4N_2$ (442.68): C, 43.41; H, 6.83; S, 28.97; N, 6.33. Found: C, 43.65; H, 6.95; S, 29.30; N, 6.24.

Bis-3,6-*O*-(*N,N*-diethylcarbamoyl)-D-glucopyranose (18). Likewise, **9** (5.0 g, 12.0 mmol) gave, after 2 h, 3.1 g (69%) of **18**. $[\alpha]_D^{27}$ +52° (*c* 1.1, CH_3OH).

Anal. Calcd for $C_{16}H_{30}O_8N_2$ (378.43): C, 50.78; H, 7.99; N, 7.40. Found: C, 50.62; H, 7.85; N, 7.35.

6-Deoxy-3-*O*-(*N,N*-diethylcarbamoyl)-6-*S*-(*N,N*-diethyldithiocarbamoyl)-D-glucopyranose (19). Likewise, **15** (5.0 g, 11.1 mmol) gave, after 2 h, 3.1 g (70%) of **19**, mp 107-109 °C; $[\alpha]_D^{27}$ +47° (*c* 1.1, CH_3OH).

Anal. Calcd for $C_{16}H_{30}O_6S_2N_2$ (410.55): C, 46.81; H, 7.36; S, 15.62; N, 6.82. Found: C, 46.80; H, 7.45; S, 15.39; N, 6.68.

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