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Synthesis of D-Mannofuranosyl-ethanethioamides and the corresponding ethanedithioate, the first *C*-glycosyl derivative with thioacylating properties.

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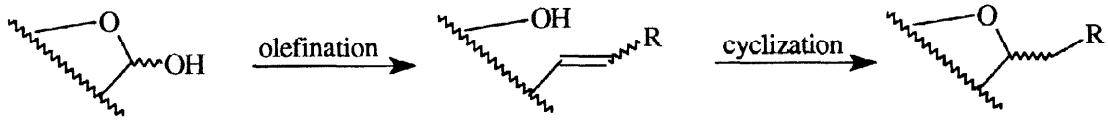
Abstract : D-Mannofuranosyl-ethanethioamides were prepared in good yields *via* a Horner-Wadsworth-Emmons reaction of thiocarbamoylmethylphosphonates with 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose. New glycosyl-ethanethioamides were obtained and one of them was converted into the corresponding dithioester which is a potential sugar substituted thioacylating agent for aminoacids.

Among the glycomimetic compounds, *C*-glycosyl derivatives have been the subject of increasing interest owing to their potential physiological activities (enzyme inhibitors)[1a,b] and their uses in organic synthesis (precursors of analogues of glycolipids or glycoproteins, chiral synthons).[2a,b] Therefore, over recent years efforts have been devoted to developing new methods[3a] for the formation of carbon-carbon bonds with diversely functionalized chains attached to the anomeric carbon. Among these methods, Wittig reactions (Ph_3P=CHR, R = CO_2R',[3b-d] CN,[3d] C(O)-thiazole[3e]) and to a lesser extent Horner-Wadsworth-Emmons (HWE) type reactions [diethylphosphonoacetate,[4a,b] diethyl(cyanomethyl)phosphonate,[4c] diethyl (phenylsulfonylmethyl)phosphonate[4d,e]] have been used. With the functionalized HWE reagents, the *C*-anomeric olefination is very often followed by an intramolecular cyclization leading to a mixture of two epimers (Moffatt procedure)[3d] (Scheme 1).



Scheme 1

Recently, a HWE reaction was used by Coutrot *et al.*[5a-c] for the olefination of aldoses bearing an exocyclic aldehyde group with functionalization by aminoacid or peptide moieties. Carbamoylmethylphosphonates prepared from phosphonoacetic acid and aminoacids or peptides were used for this purpose.

Our group has shown recently that metallated thiocarbamoylmethylphosphonates are efficient HWE reagents readily prepared by thioacylation of amines and aminoacids with ethyl phosphonodithioacetate **1**.[6] In contrast, the enethiolate of dithioester **1** is a poor olefinating reagent with aromatic aldehydes[7a,b] and we found it unreactive with 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose **2**. The choice of this protected sugar, as a model for testing the HWE reaction of thiocarbamoylmethylphosphonates with the hemiacetal functionality,

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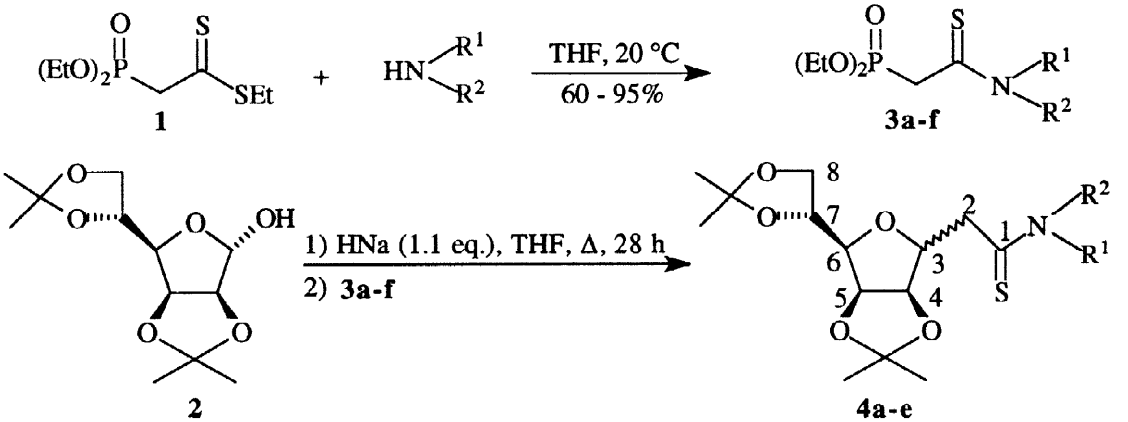
results from its accessibility (compound easy to prepare or commercially available) and its low tendency to give undesirable elimination reactions in basic medium. We describe here the reaction of **2** with the sodium salts of various thiocarbamoylmethylphosphonates which efficiently leads to new glycosyl ethanethioamides and the preparation of the corresponding dithioester.

Thiocarbamoylmethylphosphonates **3a-f** were readily prepared in good yield by reacting ethyl phosphonodithioacetate **1** with the corresponding amines, one equivalent of triethylamine being added in the case of glycine. The reaction of protected D-mannofuranose **2** with the sodium salts of the thioamides **3a-d** in THF at 60 °C led to a mixture (~2/8) of the corresponding α- and β- glycosyl ethanethioamides **4a-d** (Scheme 2). Excellent yields were obtained for compounds **4a-d** and both α and β epimers were easily separated by silica gel chromatography (EtOAc:light petroleum, 3:7) and characterized.[8]



Scheme 2

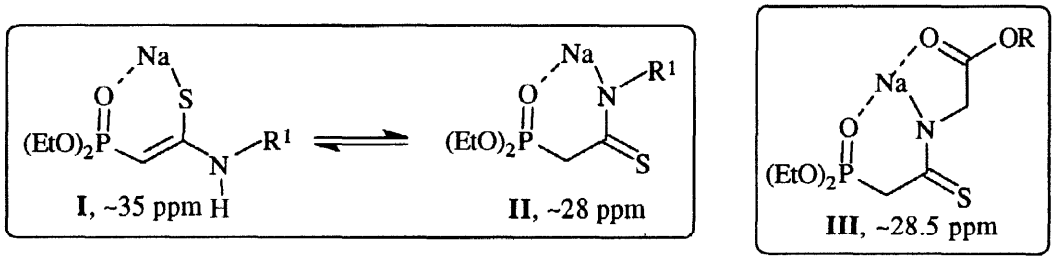
Table 1

R1	R2	thioamide 3	Yield (%)	^{31}P NMR(a) (C_6D_6)	^{31}P NMR(b) (C_6D_6)	*C*-glycoside 4	Yield (%)	α/β ratio
CH_3	H	**3a**	93	+21.7	+35.5/+28.7 (40/60) ratio	**4a**	93	21/78
$(CH_2)_7CH_3$	H	**3b**	94	+21.7	+35.7/+28.4 (45/55) ratio	**4b**	94	23/77
CH_3	CH_3	**3c**	93	+19.4	+35.1	**4c**	93	17/83
$CH_2(CH_2)_3CH_2$		**3d**	95	+19.6	+35.6	**4d**	91	15/85
CH_2CO_2Me	H	**3e**	77	+20.9	+28.2	**4e**	15	(d)
CH_2CO_2H	H	**3f**	60	+20.9	+29.7(c)	**4f**	–	–

(a) ^{31}P NMR of thiocarbamoylmethylphosphonate **3**.(b) ^{31}P NMR of **3** with 1.1 eq. of HNa.(c) ^{31}P NMR of **3f** with 2.1 eq. of HNa.(d) the α epimer could not be detected.

The disappointing results observed for **4e** and **4f** when using aminoester and aminoacid derivatives **3e** and **3f** were rather unexpected since previous work from our laboratory had shown that HWE reactions carried out on benzaldehyde with such phosphonates lead to the corresponding α, β-unsaturated thioamides in fairly good yields.[6] A comparison between the ^{31}P NMR of the metallated thiocarbamoylmethylphosphonates **3a-f** (Table 1) was performed. This demonstrated first that the enethiolate anions **I** obtained from the N,N-dialkylthioamides **3c** and **3d** exhibit signals around 35 ppm. Moreover, the sodium salts of secondary

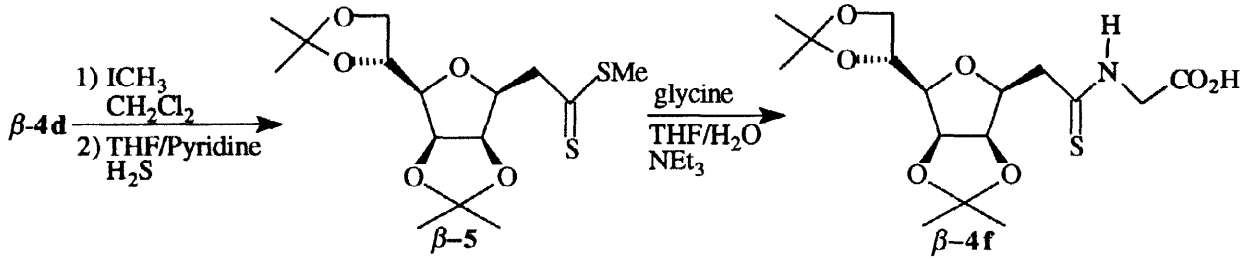
thioamides **3a** and **3b** exhibit a second signal at 28 ppm, which can be easily assigned to the amide anion **II**.[9] Such an amide-form, most probably favoured by an internal chelation of the cation by the carbonyl group (form **III**), was the only one observed at around 28.5 ppm in thioamides derived from glycine or methylglycinate (Scheme 3). Therefore in the case of both **3e** and **3f**, the extremely low concentration of the enethiolate form **I** (required for the olefination), together with the low concentration of the open-chain aldehydic form of the D-manno substrate kinetically disfavor the olefination process. Consequently, the reaction becomes extremely slow and only very low yields (< 15%) can be attained.



Scheme 3

We therefore decided to change our strategy for the grafting of the aminoacid segment onto the *C*-glycosyl moiety. Since the thiocarbamoylmethylphosphonate **3d** prepared from piperidine led to the corresponding *C*-glycosyl derivative **4d** in excellent yield, we decided to convert the thioamide **4d** into the corresponding dithioester (a function known for its thioacylating properties).[10]

Using the methylation-sulfhydrolysis method,[11a,b] β-**4d** was converted into the *C*-glycosyl-ethanedithioate β-**5**[12] in 81% yield. The thioacylating ability of β-**5** was then tested with two functionalized amino compounds : reaction of β-**5** at room temperature with methylglycinate readily produced the *C*-glycosyl derivative β-**4e**[13] in 85% yield after purification. Reacting β-**5** similarly with glycine in the presence of triethylamine gave a 80% yield of the *C*-glycosyl derivative β-**4f** (Scheme 4).



Scheme 4

Dithioester β-**5**, whose reactivity needs to be examined in further detail, is the first *C*-glycosyl derivative with thioacylating properties. The dithioester group can furthermore be used for other chemical tranformations: *C*-glycosyl derivatives such as β-**5** can, in particular, react wih a large variety of amino (or diamino) substituted compounds to give aminoacid or peptide derivatives associated with a carbohydrate moiety. The application of the present sequence of reactions to other protected sugars with free anomeric position will be also investigated.

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8. The anomeric configuration of *C*-glycosyl derivative **4** was established by ^1H and ^{13}C (250 MHz) NMR ($CDCl_3$). Expected differences were observed between the two anomers: J_{H3H4} = 3.4 Hz for anomer β (cis configuration of C_3-H and C_4-H); J_{H3H4} ~ 0 Hz for anomer α (trans configuration). In ^{13}C NMR, chemical shifts of C-2, C-3 and C-4 of anomer β are respectively 1, 2 and 4 ppm upfield compared to those of anomer α. Optical rotations were measured at 20 °C in $CHCl_3$ solutions.

	α-**4a**	β-**4a**	α-**4b**	β-**4b**	α-**4c**	β-**4c**	α-**4d**	β-**4d**	β-**4e**
$[\alpha]_D$	+67.5	-27.5	+40.2	-22.2	-14.1	-14.7	-17.6	-8.8	-28.6
mp (°C)	131	128	oil	oil	oil	118	101	88	89

The microanalyses were in good agreement with calculated values : C ± 0.40, H ± 0.05, S ± 0,25. Regioselective deprotection was carried out on β-**4d** : the 7,8-diol moiety was unmasked using Amberlyst 15 (H^+) in EtOH, while full deprotection was achieved with a Et_2O-water-CF_3CO_2H mixture.
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12. Selected NMR data for β-**5** : ^1H NMR ($CDCl_3$) : 1.33, 1.37, 1.43, 1.49 [4s, 2 $C(CH_3)_2$], 2.63 (s, SCH_3), 3.38 [d, $CH_2C(S)$, $^3J_{H2H3}$=6.3], 3.49 (dd, H_6, $^3J_{H6H7}$=5.5, $^3J_{H6H5}$=1.2), 4.06 (m, H_8), 4.20 (dt, H_3, $^3J_{H3H2}$=6.3, $^3J_{H3H4}$=1.2), 4.37 (m, H_7), 4.74 (~s, H_4 and H_5); ^{13}C NMR : 19.10 (SCH_3), 22.80, 24.44, 24.92, 26.02 [2 $C(\underline{C}H_3)_2$], 48.72 [$\underline{C}H_2C(S)$], 65.99 (C_8), 72.24 (C_7), 80.18 (C_4), 80.29 (C_5), 80.53 (C_3), 80.67 (C_6), 108.17, 111.69 [2 $\underline{C}(CH_3)_2$], 233.87 [C(S)]. $[\alpha]_D$=-45.1 ($CHCl_3$) at 20 °C, mp (°C)=81. Microanalysis for $C_{15}H_{24}O_5S_2$; Calc. : C, 51.73; H, 6.89; S, 18.39. Found : C, 51.79, H, 7.04, S, 18.57. The crude product was purified by column chromatography (silica gel; EtOAc-light petroleum, 25:75).
13. Selected NMR data for β-**4e** : ^1H NMR ($CDCl_3$) : 1.35, 1.39, 1.45, 1.50 [4s, 2 $C(CH_3)_2$], 3.09-3.26 (m, H_{2a} and H_{2b}, $^2J_{H2aH2b}$=14.9, $^3J_{H2aH3}$=8.0, $^3J_{H2bH3}$=4.5), 3.56 (dd, H_6, $^3J_{H6H7}$=7.9, $^3J_{H6H5}$=3.4), 3.96 (m, H_3), 4.09-4.20 (m, H_{8a} and H_{8b}, $^2J_{H8aH8b}$=8.8, $^3J_{H8aH7}$=6.8, $^3J_{H8bH7}$=3.6), 4.38 [m, $CH_2C(O)$], 4.43 (m, H_7), 4.71 (dd, H_4, $^3J_{H4H5}$=6.1, $^3J_{H4H3}$=3.4), 4.78 (dd, H_5, $^3J_{H5H4}$=6.1, $^3J_{H5H6}$=3.4), 8.67 (s, NH); ^{13}C NMR : 24.60, 25.29, 25.85, 27.13 [2 $C(\underline{C}H_3)_2$], 45.62 [$\underline{C}H_2C(S)$], 47.67 ($NHCH_2$), 52.75 (OCH_3), 67.04 (C_8), 72.95 (C_7), 80.14 (C_3), 80.52 (C_5), 81.30 (C_4), 82.27 (C_6), 109.38, 112.85 [2 $\underline{C}(CH_3)_2$], 169.28 [C(O)], 201.86 [C(S)]. Microanalysis for $C_{17}H_{27}NO_7S$; Calc. : S, 18.22. Found : S, 18.47. The crude product was purified by column chromatography (silica gel; EtOAc-light petroleum, 2:8) and by crystallisation from hexane.