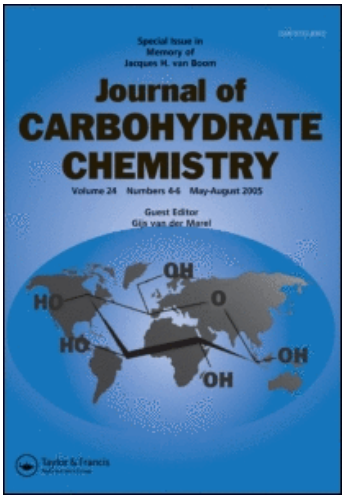

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Synthesis and Reactions of 2,3,4,6-Tetra-O-Acetyl-1-S-(N-Acylaminoacyl)-1-Thio-β-D-Glucopyranoses

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SYNTHESIS AND REACTIONS OF 2,3,4,6-TETRA-O-ACETYL-1-S-(N-ACYLAMINOACYL)-1-THIO-β-D-GLUCOPYRANOSES

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ABSTRACT

Fully acetylated 1-thio-β-D-glucopyranosyl esters of N-protected amino acids (4-13) were prepared in high yields by condensation of 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranose (1) with a pentachlorophenyl esters of N-protected amino acids (2) in the presence of imidazole, or b N-protected amino acids (3) in the presence of DCC + imidazole. High tendency of the S-acyl aglycon group in 4-13 to undergo S⟶O and S⟶N migrations was demonstrated in reactions with several alcohols and amines.

INTRODUCTION

Esters of thiolcarboxylic acids are generally much more reactive than the corresponding carboxylic acid esters[1]. Thiolesters have attained a great deal of attention as active acylating agents in biological[2] (e.g. acetyl-CoA, non-ribosomal peptide biosynthesis) and chemical[3] (e.g. peptide synthesis) reactions. 1-Thioglycosyl esters of amino acids were suggested[4] as intermediates in the base-catalysed rearrangement and

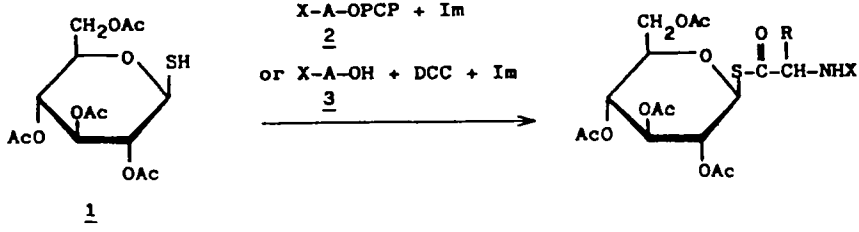
degradation reactions of glucosinolates (e.g. sinigrin) producing thioglucose, amino acid and sulphate as ultimate products. In contrast to thioglycosides[5], there is little information in the literature on the chemistry of 1-thioglycosyl esters, and only a few number of 1-thioglucosyl esters have been prepared[6,7] so far.

Various studies in this laboratory[8-10] have been concerned with the synthesis and reactions of glycosyl esters of amino acids and peptides. It has been shown that these compounds, although readily hydrolysed, may also undergo transesterification and transamination reactions through nucleophilic attack at the 1-ester carbonyl group. The present work was initiated in order to obtain some information on the hitherto unknown class of 1-thioglycosyl esters of amino acids. We now report on the synthesis and reactions of the fully acetylated 1-thio-D-glucopyranosyl esters having the carboxyl group of an N-acylamino acid linked by the thiolester bond to the sugar moiety.

RESULTS AND DISCUSSION

The imidazole-promoted active ester and dicyclohexylcarbodi-imide (DCC) methods, elaborated[8] for the preparation of the fully protected 1-O-(acylaminoacyl)--D-glucopyranoses, were successfully applied to the synthesis of the corresponding 1-thio analogues. Thus, treatment of 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranose[11,12] (1) with the respective N-acylamino acid pentachlorophenyl ester (2), or N-acylamino acid (3) and DCC, in the presence of one equivalent of imidazole, afforded (Scheme 1) crystalline 1-thioglucosyl esters 4-13 in high yields. When imidazole was omitted, only traces of the corresponding product were formed, ir-

Scheme 1



1

X-A in: 2	3		R	X
Z-Gly	-	4	H	Z
Z-L-Ala	-	5	CH_3	Z
Z-D-Ala	-	6	CH_3	Z
Boc-L-Ala	-	7	CH_3	Boc
-	Boc-D-Ala	8	CH_3	Boc
Z-L-Phe	Z-L-Phe	9	$PhCH_2$	Z
Boc-L-Phe	-	10	$PhCH_2$	Boc
-	Ac-L-Phe	11	$PhCH_2$	Ac
Z-L-Ala-Gly	-	12	CH_3	Z-$NHCH_2CO$
Z-L-Ala-L-Ala	-	13	CH_3	Z-NHCHCO (CH3)

A = amino acid residue; PCP = C_6Cl_5; Im = imidazole;
Z = $PhCH_2OCO$; Boc = $(CH_3)_3COCO$

respective of the method employed. Analytical and physical data on the compounds prepared are given in Table 1.

The IR spectra of compounds 4–13 showed the thiol ester carbonyl absorption[13] (1700-1720 cm^{-1}) well separated from that exhibited by acetoxy carbonyl groups

TABLE 1

Analytical Data of 2,3,4,6-Tetra-O-acetyl-1-S-(N-acylaminoacyl)-thio-ß-D-glucopyranoses

Compound	Yield [a] (%)	M. p. [b]	$[\alpha]_D$ [c]	Formula	Anal. Calc. (%)				Found (%)			
					C	H	N	S	C	H	N	S
4	66.5	89-91	- 6.8 [d]	$C_{24}H_{29}NO_{12}S$	51.89	5.26	2.52	5.77	51.70	5.47	2.58	5.37
5	89.4	98-101	- 5.6 [d] -16.0	$C_{25}H_{31}NO_{12}S$	52.71	5.49	2.46	5.62	52.95	5.37	2.73	5.79
6	82.2	119-121	- 8.9 [d] + 9.0	$C_{25}H_{31}NO_{12}S$	52.71	5.49	2.46	5.62	52.82	5.67	2.72	5.79
7	60.0	122-124	-40.9 [d]	$C_{22}H_{33}NO_{12}S$	49.34	6.21	2.62	5.99	49.27	6.24	2.76	6.13
8	40.0	175-176	+21.7 [d]	$C_{22}H_{33}NO_{12}S$	49.34	6.21	2.62	5.99	49.33	6.04	2.51	5.57
9	74.6 [e]	144-146	-40.7	$C_{31}H_{35}NO_{12}S$	57.67	5.46	2.17	4.96	57.39	5.74	2.07	5.09
10	94.0	147-148	-32.2	$C_{28}H_{37}NO_{12}S$	54.98	6.10	2.29	5.24	54.68	6.18	2.07	5.60
11	70.0	166-168	-36.0	$C_{25}H_{31}NO_{12}S$	54.24	5.64	2.53	5.79	54.02	5.59	2.80	6.16
12	86.9	130-132 [f]	-36.8	$C_{27}H_{34}N_2O_{13}S$	51.75	5.47	4.47	5.12	51.74	5.76	4.59	5.02
13	84.4	112-114 [f]	-40.8	$C_{28}H_{36}N_2O_{13}S$	52.49	5.66	4.37	5.01	52.57	5.81	4.54	4.92

[a] The yields refer to crystalline products. [b] From chloroform-light petroleum, if not stated otherwise. [c] In chloroform at 24-26°C, if not stated otherwise. [d] In ethyl acetate. [e] Prepared by the amino acid active ester + Im method; the yield of 9 by DCC + Im method: 80.3%, m.p. 139-141°C, $[\alpha]_D$ -43°. [f] from ethyl acetate-light petroleum.

(1750-1760 cm^{-1}) and, in the case of 11-13, from the amide I absorption at ~1650 cm^{-1}. The spectra of 3-10 revealed the thiol ester carbonyl and urethane (Z, Boc) carbonyl (1690-1730 cm^{-1}) absorptions as two close, but distinctly resolved, sharp peaks; the 1-oxygenated analogues display only one peak in this region.

The t.l.c. homogeneity and the optical rotation values of compounds 4-13 indicated that they had the β-D-configuration, and ^1H NMR data confirmed the configurational assignment. In chloroform-d, the spectra of 4-13 revealed the O-acetyl group signals in the δ 1.96-2.08 range with the chemical shift values closely similar to those observed [8-10,14] for the fully acetylated 1-oxygenated analogues; the signals assigned to H-5 (symmetrical multiplet centred at δ ~3.80), H-6' (quartet, δ 4.06-4.07) and H-6 (quartet, δ 4.27-4.29) showed coupling constants (see Experimental) consistent with the structures proposed. In accordance with the data reported by Horton et al.[7] for 1-thio-D-glucopyranose pentaacetate, the H-1 signal in all of the spectra examined appeared at a substantially higher field (~ 0.4 ppm) than the H-1 signals of the corresponding 1-O-acyl analogues. In chloroform-d, the H-1 signals could not be measured due to overlap with other ring protons. In acetone-d_6, however, it was possible[7] to identify the anomeric protons of 4-13 as doublets (δ 5.36-5.38) with large coupling constants ($J_{1,2}$ ~ 9 Hz) partly overlapped by the wide H-3 triplet.

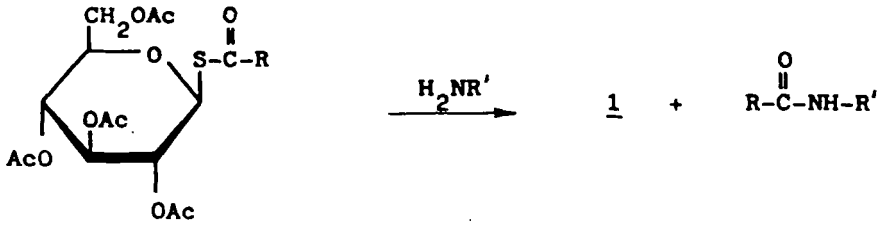
The fact that no signal corresponding to an α-D--anomeric proton could be observed in any of the above spectra, indicates that the 1-thioglucosyl esters prepared had the same configuration as the starting 1-thio sugar 1.

Treatment of compound 10 with trifluoroacetic acid at -10°C, led to a clean and rapid cleavage of the N-protecting tert-butoxycarbonyl (Boc) group to give 2,3,4,6-tetra-O-acetyl-1-S-(L-phenylalanyl)-1--thio-β-D-glucopyranose (14) as the trifluoroacetate salt. Acetylation of the latter afforded the N-acetyl derivative 11, which was also obtained by the imidazole-promoted DCC condensation of 1 and N-acetylphenylalanine.

The tendency of 1-thioglucosyl esters to act as acylating agents was examined in their reactions with some alcohols and amines. Thus, shaking of a methanolic solution of 4 with silica gel at room temperature for 3 days, led to a complete transfer of the aglycon S-acyl group to the alcoholic solvent to give N-benzyloxycarbonylglycine methyl ester in 85% yield; without silica gel, the reaction proceeded at a substantially slower rate. The silica gel catalysed S⟶O intramolecular migration of acetyl groups in 3-S-acetyl-1,2-isopropylidene-3-thio-α-D-allofuranose and related compounds was reported by Whistler et al.[15] and ascribed to the silica gel electron binding properties[16] which enhance the already high polarizability of the thiol ester carbonyl group.

A smooth S⟶O aglycon acyl migration in alkaline media was evidenced by treatment of 9 in dichloromethane with methanol in the presence of N-methylmorpholine to give N-benzyloxycarbonylphenylalanine methyl ester in high yield. In a similar fashion, when 9 was treated with methyl 2,3,4-tri-O-benzyl-β-D-glucopyranoside[17] as the alcoholic component, methyl 2,3,4-tri-O-benzyl-6-O-(N-benzyloxycarbonyl-L-phenylalanyl)-β-D-glucopyranoside (15) was isolated in 65% yield; the structure of the product was confirmed by direct synthesis. In line with the above results,

Scheme 2



12 R-C(=O) = Z-Ala-Gly- H_2NR' = H-Gly-Phe-OMe

treatment of compounds 4–13 with various molar ratios of sodium methoxide in methanol, led to parallel deacetylation and splitting of the 1-thioglucosyl ester bond under formation of the corresponding N-acylamino acid methyl ester.

The equilibrium for the aminolysis of thiol esters lies much further to the side of the acylamino derivatives[1]. Accordingly, compound 9 in dichloromethane reacted smoothly with piperidine into the corresponding N-acylamine. The susceptibility of the 1-thioglucosyl ester bond toward the amino group of a second amino acid was examined on compound 12, having the dipeptide residue as aglycon group. Thus, treatment of 12 in dichloromethane with glycyl-L-phenylalanine methyl ester as the nucleophile, at room temperature, led to S⟶N acyl migration to give (Scheme 2) the corresponding N-protected tetrapeptide methyl ester in 80% yield.

EXPERIMENTAL

General Procedures. Column chromatography was performed on Silica Gel (Merck 0.05–0.2 mm) and t.l.c. on Silica Gel 60 (Merck); solvents used were: A, ben-

zene-ethyl acetate (different proportions); B, ether--light petroleum (3:1). Detection on t.l.c. plates was effected by charring with sulphuric acid, or the chlorine-iodine reagent[18] for peptides. ^{1}H NMR spectra were obtained from a Jeol FX 90 Q FT spectrometer using $(CH_3)_4Si$ (0 ppm) as the internal standard. IR spectra were recorded with a Perkin-Elmer 297 spectrometer.

2,3,4,6-Tetra-O-acetyl-1-S-(N-acylaminoacyl)-1--thio-β-D-glucopyranoses (4-13). a To a solution of 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranose[11,12] (1) (364 mg, 1 mmol) and the appropriate N-acylamino acid pentachlorophenyl ester[3] (2) (1.1 mmol) in CH_2Cl_2 (60 ml) was added imidazole (68 mg, 1 mmol) at room temperature with shaking, and the reaction mixture was kept (monitoring by t.l.c. in solvent A, 1:1 or 1:2) at room temperature for 4-6 h; reaction time for 12 and 13 was ~16 h. Pentachlorophenol was filtered off, and the filtrate was washed with water, 10% citric acid in water, water, aqueous $NaHCO_3$ and water, dried and concentrated. Direct crystallization of the residue afforded the title compounds 4-6 and 9-10, respectively; purification of 12 and 13 was effected on silica gel columns with solvent A (1:1), followed by crystallization. The yields and physical and analytical data of the products are given in Table 1.

b To a solution of 1 (1 mmol) and the appropriate N-acylamino acid (3) (1 mmol) in CH_2Cl_2 (60 ml) was added under shaking DCC (1 mmol) and imidazole (1.1 mmol), and the reaction mixture (monitoring by t.l.c.) was kept at room temperature for 4-6 h. N,N'-Dicyclohexylurea was filtered off, and the filtrate was further treated as described above. After evaporation of the solvent, compounds 7-9 and 11

were obtained by direct crystallization of the residue.

^{1}H NMR Data of 6 in $CDCl_3$: δ 5.38-5.12 (6H, H-1, 2,3,4 + $OCOCH_2Ph$), 4.29 (q, $J_{5,6}$ 4.2 Hz, $J_{6,6'}$ 11 Hz, H-6), 4.06 (q, $J_{5,6'}$ 2.5 Hz, H-6'), 3.91-3.75 (m, J 16 Hz, H-5), 2.06 (s, CH_3CO), 2.02 (s, CH_3CO), 2.00 (s, 2 x CH_3CO), 1.40 (d, J 8 Hz, CH_3CH). In $(CD_3)_2CO$: δ 5.36 (d, $J_{1,2}$ 9 Hz, H-1), 5.41 (t, $J_{2,3} = J_{3,4}$ 10 Hz, H-3), 5.17-4.95 (4H, H-2,4 + $OCOCH_2Ph$). ^{1}H NMR data of 7 in $CDCl_3$: δ 5.30-4.92 (m, H-1,2,3,4), 4.27 (q, $J_{5,6}$ 4.5 Hz, $J_{6,6'}$ 12 Hz, H-6), 4.06 (q, $J_{5,6'}$ 3 Hz, H-6'), 3.92-3.71 (eight-peak m, H-5), 2.07 (s, CH_3CO), 2.03 (s, CH_3CO), 2.01 (s, 2 x CH_3CO), 1.45 (s, Me_3C), 1.38 (d, J 8 Hz, CH_3CH). In $(CD_3)_2CO$: δ 5.37 (d, $J_{1,2}$ 9 Hz, H-1), 5.40 (t, $J_{2,3}$ 10 Hz, H-3), 5.15-4.91 (m, H-2,4).

2,3,4,6-Tetra-O-acetyl-1-S-(L-phenylalanyl)-1-thio-β-D-glucopyranose Trifluoroacetate Salt (14). To compound 10 (100 mg) was added trifluoroacetic acid (98%, 0.5 ml) at -10°C ; after 10 min, anhydrous ether (15 ml) was added, the solution was concentrated, and traces of CF_3CO_2H were removed by co-distillation with ether. Dissolution of the residue in EtOAc, followed by addition of light petroleum at 0°C, deposited 14 (76.5 mg, 75%) as a chromatographically homogenous hygroscopic solid. ^{1}H NMR ($CDCl_3$): δ 7.30 (Ph), 2.11 (s, CH_3CO), 2.08 (s, CH_3CO), 2.02 (s, 2 x CH_3CO).

Anal. Calc. for $C_{25}H_{30}F_3NO_{12}S$: C, 48.00; H, 4.83; N, 2.24; S, 5.13. Found:C, 47.98; H, 5.20; N, 2.37; S, 4.69.

To a cooled solution (0°C) of the freshly prepared 14 (100 mg) in water (15 ml) was added 20% Ac_2O in acetone (15 ml), and the solution was kept at 0°C

for 24 h. After removal of traces of Ac_2O by co-distillation with water (0.1 Torr), the residue was crystallized from CH_2Cl_2-light petroleum to give the N-acetyl derivative 11 (74 mg, 84%), m.p. 168–170°C, which ^1H NMR spectrum was indistinguishable from that of 11 prepared by imidazole-promoted DCC condensation.

S→O Acyl Migrations. a. To a solution of compound 4 (111 mg) in CH_3OH (1 ml) was added silica gel (200 mg), and the mixture was shaken for 3 days at room temperature, whereafter 4 (t.l.c.) had practically disappeared. The residue obtained by evaporation was passed through a silica gel column (solvent B) to give first Z-Gly-OMe[19] (38 mg, 85%), ^1H NMR ($CDCl_3$): δ 7.23 (Ph), 5.96 (t, NH), 5.00 (s, $OCOCH_2Ph$), 3.56 (OCH_3). Eluted second was the thiosugar 1 (54.6 mg, 75%).

b. Identical treatment of 4, but in the absence of silica gel, gave, upon column chromatography, unchanged 4 (87 mg, 78.4%) and small amounts of Z-Gly-OMe and 1 (~10% each).

c. To compound 9 (100 mg) in CH_2Cl_2 (10 ml) were added N-methylmorpholine (0.5 ml) and CH_3OH (2 ml), and the mixture was kept for 24 h at 40°C. The residue left after evaporation of the solvent was passed through silica gel (solvent B) to give Z-Phe-OMe[8] (43 mg, 89%), followed by 1 contaminated with its decomposition products.

d. To 9 (100 mg) in CH_2Cl_2 (10 ml) were added N-methylmorpholine (0.5 ml) and methyl 2,3,4-tri-O-benzyl-β-D-glucopyranoside[17] (217 mg, 3 equivs), and the reaction mixture was kept for 10 days at 40°C. After concentration, the residue was passed through silica gel (solvent A, 3:1) to give homogenous methyl 2,3,4-tri-O-benzyl-6-O-(N-benzyloxycarbonyl-L-phenyl-

alanyl)-β-D-glucopyranoside (15)(66 mg, 57%) which m.p., $[\alpha]_D$ and ^{1}H NMR spectrum were indistinguishable from that prepared by direct synthesis.

Aminolysis reactions. a. To compound 9 (100 mg) in CH_2Cl_2 (15 ml) was added piperidine (40 µl, 2.5 equivs); after 5 h at room temperature, the reaction mixture was worked-up as described for preparation of 4-13, and the residue was passed through silica gel (solvent A, 3:1) to give N-benzyloxycarbonyl-L-phenylalanine piperidide (45.5 mg, 80%), m.p. 65-67°C (from light petroleum); lit.[20]: m.p. 66-68°C. ^{1}H NMR ($CDCl_3$) δ 7.32-7.20 (2 x Ph), 5.08 (s, $OCOCH_2Ph$), 3.41-3.52 (m, 2 x CH_2), 2.98 (d, J 7 Hz, $CHCH_2Ph$), 1.46 (broad s, 3 x CH_2).

b. To a stirred suspension of HClxH-Gly-Phe-OMe (409 mg, 1.5 mmol) in CH_2Cl_2 (25 ml) was added at room temperature N-methylmorpholine (0.17 ml, 1.5 mmol), followed by 1-thioglucosyl ester 12 (313 mg, 0.5 mmol), and stirring was then continued for further 16 h. EtOAc (25 ml) was added, and the reaction mixture was worked-up as described for preparation of 3-14. After removal of the solvent, the residue was dissolved in hot CH_2Cl_2; addition of light petroleum to the cooled solution precipitated Z-Ala-Gly-Gly-Phe--OMe (199 mg, 80%). A second crystallization afforded the analytically pure compound, m.p. 156-158°. ^{1}H NMR (DMSO-d_6), δ 7.26, 7.15 (2 x Ph), 4.93 (s, $OCOCH_2Ph$), 3.53 (s, OCH_3), 1.20 (d, J 7 Hz, CH_3CH).

Anal. Calc. for $C_{25}H_{30}N_4O_7$: C, 60.23; H, 6.07; N, 11.24. Found: C, 59.99; H, 6.32; N, 10.98%.

Methyl 2,3,4-Tri-O-benzyl-6-O-(N-benzyloxycarbonyl-L-phenylalanyl)-β-D-glucopyranoside (15). To a solution of methyl 2,3,4-tri-O-benzyl-β-D-glucopyranoside (144 mg) in CH_2Cl_2 (15 ml) were added Z-Phe-

-OPCP (186 mg) and imidazole (46 mg, 2 equivs), and the reaction mixture was left at room temperature for 24 h. After work-up, as described for 4-13, the crude product was crystallized from di (2-propyl) ether + some drops of light petroleum to give 15 (150 mg, 65%), m.p. 99-101°C, $[\alpha]_D$ +24° (c 1, $CHCl_3$). ^1H NMR ($CDCl_3$), δ 7.1-7.3 (5 x Ph), 5.00 (s, $OCOCH_2Ph$), 3.5 (s, OCH_3), 3.04 (d, J 6 Hz, $CHCH_2Ph$).

Anal. Calc. for $C_{45}H_{47}O_9N$: C, 72.46; H, 6.35; N, 1.88. Found: C, 72.71; H, 6.41; N, 1.91%.

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REFERENCES

1. M. J. Janssen in: "The Chemistry of Carboxylic Acids and Esters" (Ed., S. Patai), Interscience Publishers, London, 1969, p. 705.

2. F. Lipmann, Acc. Chem. Res., 6, 361 (1973).

3. M. Bodanszky in: "The Peptides", Vol. 1 (Eds., E. Gross and J. Meienhofer), Academic Press, New York, N. Y., 1979. p. 105.

4. P. Friis, P. O. Larsen, and C. E. Olsen, J. Chem. Soc., Perkin Trans. I, 1977, 661.

5. D. Horton and D. H. Hutson, Adv. Carbohydr. Chem., 18, 123 (1963).

6. J. Kocourek, Collect. Czech. Chem. Commun., 29, 316 (1964).

7. C. V. Holland, D. Horton, M. J. Miller, and N. S. Bhacca, J. Org. Chem., 32, 3077 (1967).

8. D. Keglević, A. Kornhauser, and Š. Valenteković, Carbohydr. Res., 22, 245 (1972).

9. Š. Valenteković and D. Keglević, Carbohydr. Res., 47, 35 (1976).

10. D. Keglević, M. Pongračić, and J. Horvat, Carbohydr. Res., 80, 63 (1980).

11. M. Černy and J. Pacek, Collect. Czech. Chem. Commun., 26, 2084 (1961).

12. D. Horton, Methods Carbohydr. Chem., 2, 433 (1963).

13. D. Horton and M. L. Wolfrom, J. Org. Chem., 27, 1794 (1962).

14. J. Horvat and D. Keglević, Carbohydr. Res., 75, 117 (1979).

15. R. L. Whistler, A. K. N. Anisuzzaman, and J. C. Kim, Carbohydr. Res., 31, 237 (1973).

16. V. S. Joshi, N. P. Damodaran, and S. Dev, Tetrahedron, 27, 475 (1971).

17. D. Keglević and Dj. Ljevaković, Carbohydr. Res., 64, 319 (1978).

18. H. N. Rydon and P. W. G. Smith, Nature, 169, 922 (1952).

19. H. Weygand, W. Steglich, and W. Oettmeier, Chem. Ber., 103, 1655 (1970).

20. H. Gregory, A. H. Laird, J. S. Morley, and J. M. Smith, J. Chem. Soc (C), 1968, 522.