Tetrahedron Vol. 48, No. 15, pp. 3061-3068, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00
Pergamon Press Ltd

AMPHIPHILIC AND MESOGENIC CARBOHYDRATES -II. SYNTHESIS AND CHARACTERISATION OF MONO-O-(n-ALKYL)-D-GLUCOSE DERIVATIVES[1]

Ralf Miethchen*, **Jens Holz**, **Heiko Prade**
Department of Organic Chemistry, University of Rostock,
Buchbinderstraße 9, D-2500 Rostock, Germany

Andras Liptak
Institute of Biochemistry, Lajos-Kossuth-University of Debrecen
P.O.B. 55, H-4010 Debrecen, Hungary

(*Received in Germany* 25 *November* 1991)

Keywords: Mesogenics, amphiphilic glucoses, mono-O-(n-alkyl)-D-glucopyranoses

Abstract: The synthesis of various amphiphilic O-(n-alkyl)-D-glucopyranoses, having the long alkyl chain (C_8H_{17} - $C_{16}H_{33}$) in 2-, 3-, 4- or 6-position are described. The investigations of the thermal behaviour of 6-O-(**13a-e**), 4-O-(**14a-e**), 3-O-(**15a-e**) and 2-O-(n-alkyl)-D-glucopyranoses (**16a-e**) and the corresponding methyl-α-D-glucosides **4a-e**, **8a-e** and **12a-e**, respectively, are summarized in this paper.

INTRODUCTION

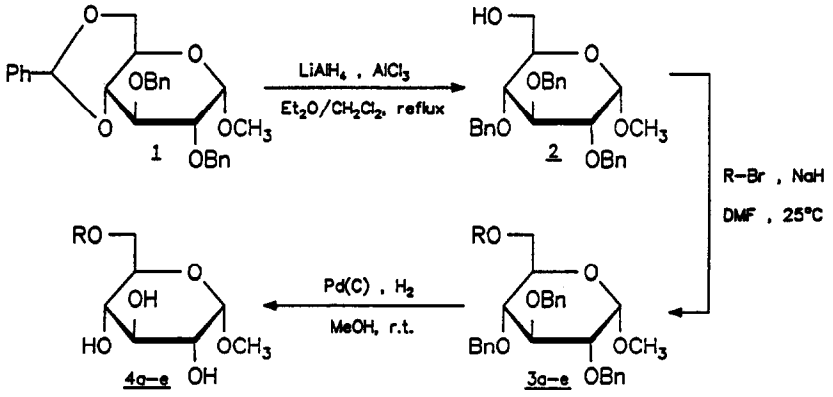
Despite the long knowledge about the existence of liquid crystalline compounds the investigations of the potential carbohydrate derivatives were intensified only in the last decade.[2a] Most of the hitherto described derivatives are the 1-O-(n-alkyl)-α/β-glycopyranosides[2b,3,4,5,6] and the 1-S-analogous compounds.[5,6,7] Furthermore, the 1,1-dithioacetals of several aldoses,[8,9,10a] amphiphilic alditoles,[10b,11] D-gluconamides[12,13] and 4,6-O-(n-alkylidene)-D-glucopyranoses[1b] were investigated by several research groups. A systematical survey of the thermotropical behaviour of monosaccharides containing one or more long alkyl chains at various sites has not been carried out yet.

The object of our research for this report was to detect the relations between the structure of a D-glucose mesogen and the temperature range, where a mesophase is formed. We studied homologous series of 2-O-(n-alkyl)-, 3-O-(n-alkyl)-, 4-O-(n-alkyl)- and 6-O-(n-alkyl)-D-gluco-

pyranoses, including the 1-O-methyl derivatives. Recently, we reported also on the mesogenic properties of some di-O- and tri-O-(n-alkyl)-D-glucopyranoses.[1a,14]

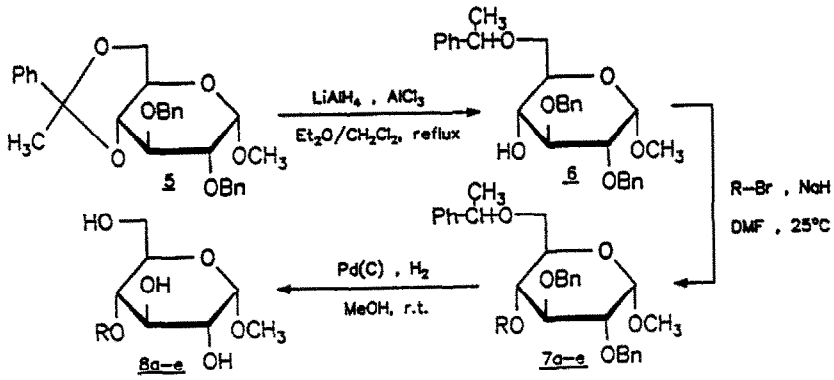
DISCUSSION AND RESULTS

Methyl-6-O-(n-alkyl)-D-glucopyranosides: The methyl-2,3-di-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside **1** described by Zemplen[15] was used to prepare the methyl-6-O-(n-alkyl)-α-D-glucopyranosides **4a-e**. Firstly, **1** was converted to the 2,3,4-tri-O-benzyl derivative **2** by means of lithium aluminium hydride and aluminium chloride[16] and than alkylated to give **3a-e**. Finally, the products **4a-e** could be obtained in good yields by the hydrogenation of **3a-e** (scheme 1).



Scheme 1. Synthesis of the methyl-6-O-(n-alkyl)-α-D-glucopyranosides **4a-e**

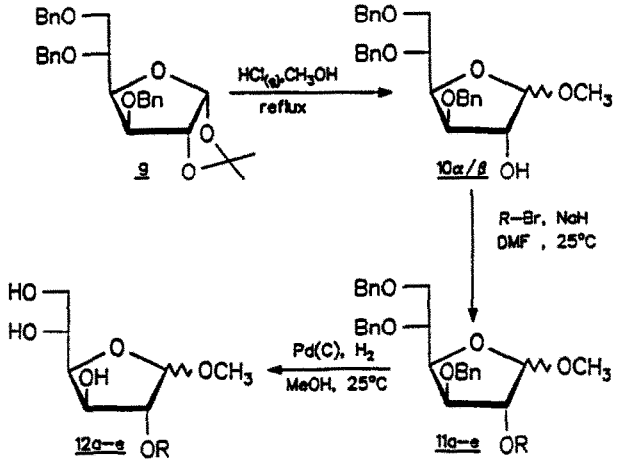
Methyl-4-O-(n-alkyl)-D-glucopyranosides: We used a selective hydrogenolytic ring cleavage of ketals[17] to prepare the carbohydrate derivative **6** which is unprotected in the 4-position. In this case the methyl-2,3-di-O-benzyl-α-D-glucopyranoside[18] was converted into the derivative **5** with acetophenone dimethylketal[19] (scheme 2). The compound **1** differs from **5** in the orientation of the phenyl group at the 1,3-dioxane ring (equatorial arrangement in **1**, axial in **5**). This is the cause of the different reactivity of these two compounds under analogous conditions ($LiAlH_4$, $AlCl_3$). The methyl-6-O-(methylphenyl)methyl-2,3-di-O-benzyl-α-D-glucopyranoside **6** was alkylated to the compounds **7a-e** and the following hydrogenation yields the methyl-4-O-(n-alkyl)-α-D-glucopyranosides **8a-e**.



R = a: C_8H_{17}, b: $C_{10}H_{21}$, c: $C_{12}H_{25}$, d: $C_{14}H_{29}$, e: $C_{16}H_{33}$

Scheme 2. Synthesis of the methyl-4-O-(n-alkyl)-α-D-glucopyranosides **8a-e**

Methyl-2-O-(n-alkyl)-D-glucofuranosides: The 2-O-alkylated derivatives **12c-e** and **11c-e** were prepared starting with the 3,5-isopropylidene-3,5,6-tri-O-benzyl-α-D-glucofuranoside **9**.[20] One obtains from this the anomeric mixture of the methyl-D-glucofuranosides **10α** and **10β** by the acid-catalyzed methanolysis.[20] These 2-O-unprotected derivatives were alkylated to **11a-e** and subsequently debenzylated to give the methyl-2-O-(n-alkyl)-D-glucofuranosides **12a-e** (scheme 3).



α–anomer: R = c: $C_{12}H_{25}$, e: $C_{16}H_{33}$

β–anomer: R = a: C_8H_{17}, b: $C_{10}H_{21}$, d: $C_{14}H_{29}$

Scheme 3. Synthesis of the methyl-2-O-(n-alkyl)-α/β-D-glucofuranosides **12a-e**

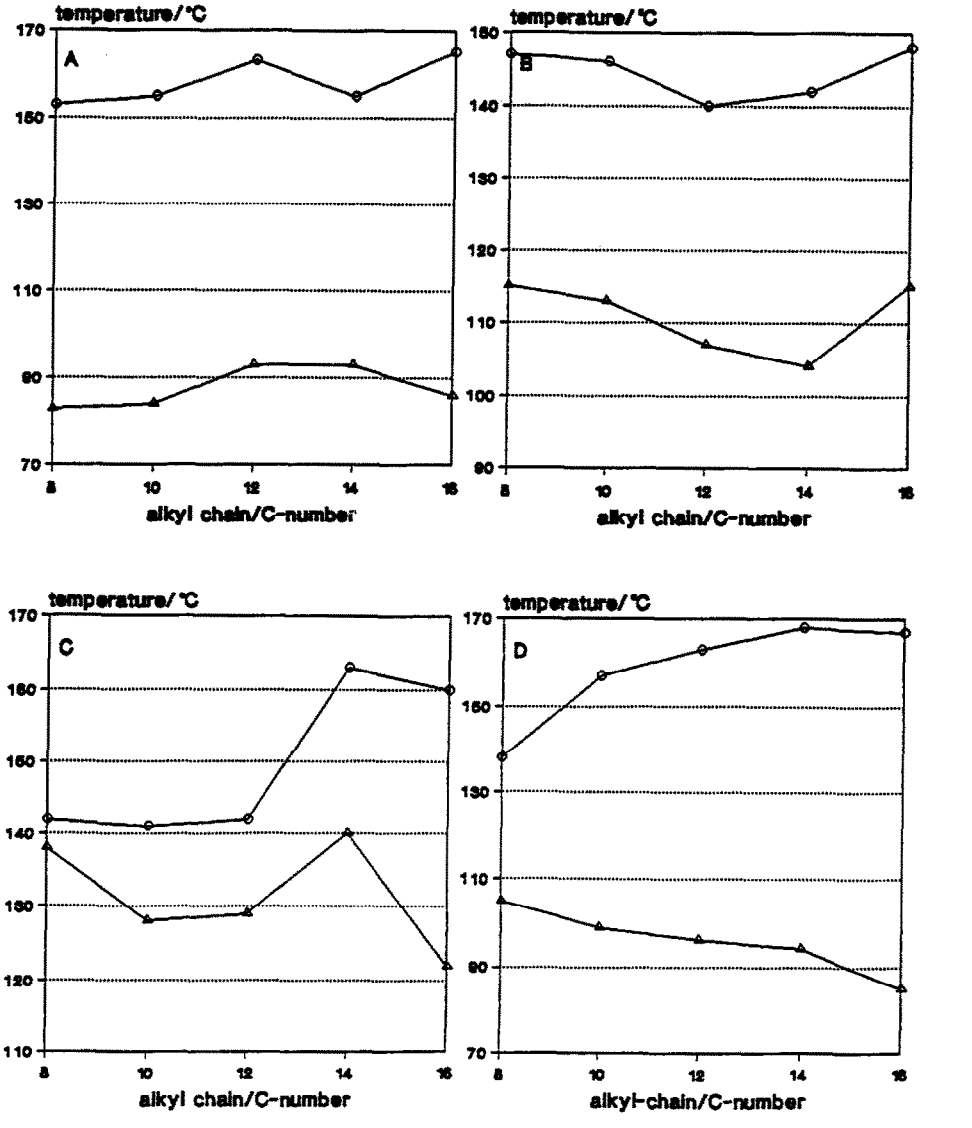
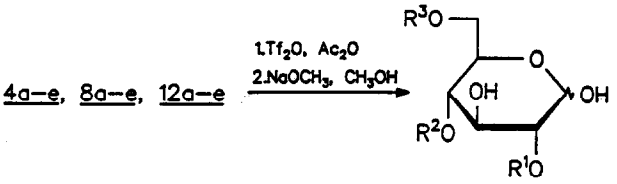


Figure 1. The thermal behaviour of the mono-O-(n-alkyl)-D-glucopyranoses investigated with the help of a Boetius micro heating stage

The cleavage of the methylglucosides **4a–e**, **8a–e** and **12a–e** to prepare **13a–e**, **14a–e** and **16a–e** did not run without problems. The attempt to remove the methoxy group in diluted hydrochloric acid failed[21] because of the lower solubility of the amphiphilic derivatives in aqueous systems. Better results (but not satisfactory) could be obtained by use of 60% aqueous trifluoroacetic acid. The t.l.c. indicated the presence of by-products (probably partial acetylated products).

We got the best results by treatment of the methyl-α-D-glucosides with the system triflic acid anhydride/acetic acid anhydride analogous to Angibeaud and co-worker.[22] The unprotected compounds **13a–e**, **14a–e** and **16a–e** could be obtained in yields of about 75% (scheme 4).

The synthesis of the 3-O-(n-alkyl)-D-glucopyranoses **15a–e** were already described in a former publication.[23]



13a–e: $R^3 = C_nH_{2n+1}$, $R^1 = R^2 = H$

14a–e: $R^2 = C_nH_{2n+1}$, $R^1 = R^3 = H$

16a–e: $R^1 = C_nH_{2n+1}$, $R^2 = R^3 = H$

R = a: C_8H_{17}, b: $C_{10}H_{21}$, c: $C_{12}H_{25}$, d: $C_{14}H_{29}$, e: $C_{16}H_{33}$

Scheme 4. Cleavage of the acetal function

The investigations of the thermotropic behaviour were carried out with a polarizing microscop. Whereas the monoalkylated methyl-α/β-D-glucosides **4a–e**, **8a–e** and **12a–e** did not form a mesogenic phase, the unprotected derivatives **13a–e**, **14a–e**, **15a–e** and **16a–e** are liquid crystalline. The mesophase type could be determined as a smectic A one by view of the fan texture. The mesophases of the prepared mono-O-alkyl-D-glucopyranoses turned out to be miscible among one another and with the one from 6-O-(n-hexyl)-D-galactopyranose (contact method). The thermal behaviour of the derivatives **13a–e**, **14a–e**, **15a–e** and **16a–e** (curves of melting and clear points) are given in figure 1. We found that the homologous 3-O-(n-alkyl)-D-glucopyranoses **15a–e** form the narrowest mesogenic phase range at all, whereas the 6-O-(n-alkyl)-D-glucopyranoses **13a–e** give the greatest differences between the melting and clear points. We recognize during the

investigations of the thermal behaviour that the melting point is not sharp and the products are already highly viscous without any visible changes in the crystals at a lower temperature as we determined for the melting point. Some more exact values were obtained by D.S.C.-measurements. The results of the both measurements (polarizing microscopy, D.S.C.) are given in the table 1; the ^{1}H-n.m.r.-spectroscopical data of the anomeric protons and the optical rotations of the investigated compounds are also summarized in this table. The ^{13}C-n.m.r. data are to find in the table 2.

EXPERIMENTAL

The t.l.c. and the column chromatography were carried out by use of t.l.c.-aluminium foil Silicagel 60 F_{254} (Merck) and Silicagel 60 (63-200 μm, Merck), respectively. The following systems were used as eluents:

system A: dichloromethane / acetone 95:5
system B: dichloromethane / acetone 7:3
and system C: dichloromethane / acetone 1:1

The hydrogenation was catalyzed by palladium on char-coal (10%, Merck). The n.m.r.-spectroscopy was carried out with a WP-200 SY and a Bruker AC-250, respectively. A Perkin Elmer 241 or a Polamat A (Carl-Zeiss-Jena) were used for the determination of the optical rotations. The melting and clear points were determined with a micro heating stage of Boetius (polarisation filter). The D.S.C.-measurements were carried out with a Mettler TA 3000 DSC 30 S instrument.
The deviations of the measured values from the elementary analysis are less than ± 0.5% compared to the calculated ones from the compounds **4a-e**, **8a-e**, **12a-e**, **13a-e**, **14a-e**, **15a-e** and **16a-e**.

General procedure for the O-alkylations
10 mmol of the monohydroxy derivative **2**, **6** or **10** and 12 mmol of the corresponding n-alkyl bromide were dissolved in 100 ml dry DMF. 1.6 g (40 mmol) sodium hydride was added to the solution at 0°C. The stirring has been continued for 10-15 hs at room temperature. After indication of the complete reaction by t.l.c. (system A) the excess of sodium hydride was decomposed by careful adding of 5 ml methanol. When the development of hydrogen was finished about 10 ml water was added to the solution. After evaporation of the solvents at 65-70°C the residue was dissolved in 150 ml dichloromethane. The inorganic products and the rest of DMF could be removed by washing with water.
After treatment of the organic phase with sodium sulfate the dichloromethane was removed on the rotary evaporator. Starting material indicated by t.l.c. could be separated by means of column chromatography (system A); yields 80-90%.

Preparation of methyl-O-(n-alkyl)-α/β-D-glucosides 4a-e, 8a-e and 12a-e
10 mmol of the derivatives **3a-e**, **7a-e** or **11a-e** were dissolved in 50 ml dry methanol and 0.45 g palladium on char-coal was added. These mixture was stirred under hydrogen athmosphere overnight; the t.l.c. (system B) indicated than the absence of the starting material. After filtration and evaporation the residue was purified by flash chromatography (system B); yields 65-80 %.

Table 1. Melting points, clear points, optical rotations and ^{1}H-n.m.r.-data (anomeric protons)

comp.	m.p. °C	$[\alpha]_D$[a]	α/β-anomer δ(H-1)[b] ppm	comp.	Boetius-data m.p.(c.p.) °C	D.S.C.-data m.p.(c.p.) °C	α/β-anomer δ(H-1)[b] ppm
4a	-	+102°(1.0)		**13a**	80- 85(153)	89.2(160.5)	
4b	42-44	+ 93°(0.9)		**13b**	82- 86(155)		4.86(α)
4c	59-61	+ 82°(0.4)	4.48(α)	**13c**	92- 94(163)		4.24(β)
4d	62-64	+ 78°(0.4)		**13d**	91- 93(155)	94.7(158.8)	
4e	68-70	+ 66°(0.3)		**13e**	85- 86(165)		
8a	48-52	+128°(1.3)		**14a**	103-105(140)		
8b	52-55	+ 99°(0.6)		**14b**	113-115(146)	115.2(147.2)	4.88(α)
8c	62-63	+ 96°(0.5)	4.50(α)	**14c**	106-109(140)		4.25(β)
8d	69-70	+ 82°(0.8)		**14d**	102-105(142)		
8e	72-74	+ 79°(0.4)		**14e**	114-115(148)		
12a	-	- 27°(0.6)		**16a**	104-105(138)	104.6(137.8)	
12b	-	- 22°(1.0)		**16b**	99-101(157)	102.5(160.5)	5.07(α)
12c	-	+ 50°(1.0)		**16c**	95- 97(163)	92.5(167.2)	4.33(β)
12d	46-47	- 32°(0.8)	4.68(β)	**16d**	94- 95(168)	99.2(173.9)	
12e	55-56	+ 52°(0.2)	4.88(α)	**16e**	85- 86(167)	93.2(165.2)	
				15a	138-140(142)	139.4(142.2)	
				15b	127-130(141)		
				15c	126-129(142)	127.5(141.8)	4.26(β)
				15d	138-142(163)	138.9(162.7)	
				15e	121-123(160)	122.0(161.3)	

a) in methanol, 20°C, parentheses: concentration in g/100 ml of solution;
b) in DMSO-d_6, TMS; deviation within a homologous series $\Delta\delta = \pm$ 0.05 ppm.

Table 2. ^{13}C-n.m.r.-data of the mono-O-(n-alkyl)-D-glucopyranoses **13a-e**, **14a-e**, **15a-e** and **16a-e** as well as the corresponding methyl-α-D-glucosides **4a-e**, **8a-e** and **12a-e** (in DMSO-d_6, TMS, δ in ppm)[a]

	4a-e	**8a-e**	**12a-e** α	**12a-e** β	**13a-e** α	**13a-e** β	**14a-e** α	**14a-e** β	**15a-e** β	**16a-e** α	**16a-e** β
C-1	99.5	99.6	101.3	107.7	92.2	96.8	92.2	96.9	97.0	89.7	96.4
C-2	74.4[c]	73.3[d]	85.6	88.8	72.2[g]	74.7[k]	72.7[l]	75.2[m]	74.6	80.1	82.9
C-3	72.0[c]	71.6[d]	77.6[e]	81.0[f]	73.1[g]	75.2[k]	73.1[l]	76.7[m]	85.2	71.8[n]	76.3[o]
C-4	71.1[c]	78.1	74.0[e]	73.0[f]	70.7[h]	70.4[h]	78.5	78.2	69.8	70.5	70.3
C-5	70.2[c]	71.3[d]	70.0	69.9	70.3[h]	76.7[k]	70.9[l]	75.5[m]	76.8	71.5[n]	75.8[o]
C-6	70.4	60.5	63.1	63.6	70.6[i]	70.6[i]	60.8	60.8	61.2	60.9	60.9
OCH_3	55.2	54.3	54.6	54.7	-	-	-	-	-	-	-
αCH_2	72.1	72.1[d]	70.0	69.2	70.5[i]	70.5[i]	71.7	71.7	72.0	69.4	71.4
CH_2	22.3- 31.5	22.1- 31.3	22.2- 31.4	22.2- 31.4	22.1- 31.3	22.1- 31.3	22.2- 31.4	22.2- 31.4	22.1- 31.3	21.8- 31.1	21.8- 31.1
CH_3	14.1	13.9	13.9	13.9	13.9	13.9	14.1	14.1	14.0	13.6	13.6

a) deviation within the homologoues series $\Delta\delta = \pm$ 0.05 ppm; b) in $CDCl_3$;
c-o) assignment may have to be reversed.

Preparation of O-(n-alkyl)-D-glucopyranoses 13a-e, 14a-e, 15a-e and 16a-e
The cleavage of the acetal function in the anomeric position of **4a-e**, **8a-e** and **12a-e** was carried out by means of the method of Angibeaud and co-worker;[22] yields > 75% after purification with the help of flash chromatography (system C).

Acknowledgements: The authors thank Prof. Dr. C. Pedersen (Technical University of Danmark, Lyngby) for the kind support on the n.m.r.-measurements as well as Prof. Dr. K. Praefcke (Technische Universität Berlin) and his group for D.S.C.-measurements and helpful discussions. Furthermore, we thank the Schering AG Berlin, the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for the financial support.

REFERENCES

1. a) Excerpt of a lecture given at the "XI. Meeting on Organic Chemistry", 1991, Copenhagen; b) Part I : Thiem, J.; Vill, V.; Miethchen, R.; Peters, D., *J. prakt. Chem.* **1991**, *333*, 173.
2. a) Jeffrey, G.A., *Acc. Chem. Res.* **1987**, *19*, 168; b) Jeffrey, G.A.; Bhattacharje, S., *Carbohydr. Res.* **1983**, *115*, 53.
3. Vill, V.; Böcker, T.; Thiem, J.; Fischer, F., *Liquid Crystals*, **1989**, *6*, 349.
4. Dahlhoff, W.V., *Synthesis* **1987**, 366.
5. Jeffrey, G.A., *Mol. Cryst. Liq. Cryst.* **1984**, *10*, 221.
6. van Doren, H.A.; van der Geest, R.; van Bolhuis, F.; Kellogg, R.M.; Wynberg, H., *Carbohydr. Res.* **1989**, *194*, 79.
7. van Doren, H.A.; van der Geest, R.; Kellogg, R.M.; Wynberg, H., *Carbohydr. Res.* **1989**, *194*, 71.
8. van Doren, H.A.; van der Geest, R.; Keuning, C.A.; Kellogg, R.M.; Wynberg, H., *Liquid Crystals* **1989**, *5*, 265.
9. Praefcke, K.; Levelut, A.-M.; Kohne, B.; Eckert, A., *Liquid Crystals* **1989**, *6*, 263.
10. a) Dahlhoff, W.V., *Z. Naturforsch.* **1987**, *42b*, 661; b) Dahlhoff, W.V., *Z. Naturforsch.* **1988**, *43b*, 1367; *Z. Naturforsch.* **1989**, *44b*, 1105;
Liebigs Ann. Chem. **1990**, 811.
11. Köll, P.; Oelting, M., *Angew. Chem.* **1986**, *98*, 362; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 368.
12. Pfannemüller, B., *Starch/Stärke* **1988**, *40*, 476.
13. Jeffrey, G.A.; Maluszynska, H., *Carbohydr. Res.* **1990**, *207*, 211.
14. Miethchen, R.; Holz, J.; Prade, H., Colloid Polym. Sci. submitted for publication;
Holz, J., Dissertation, Universität Rostock, **1992**.
15. Zemplen, G.; Csüros, Z.; Angyal, S., *Ber.* dtsch. chem. Ges. **1937**, *70*, 1848.
16. Liptak, A.; Jodal, I.; Nanasi, P., *Carbohydr. Res.* **1975**, *4*, 1.
17. Liptak, A.; Fügedi, P., *Angew. Chem.* **1983**, *95*, 245; *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 254.
18. Bell, D.J.; Lorber, J., *J. Chem. Soc.* **1940**, 453.
19 Liptak, A.; Kerekgyarto, J.; Szurmai, Z., *Carbohydr.Res.* **1988**, *175*, 241.
20. Huber, G.; Rossi, A., *Helv. Chim. Acta* **1968**, *51*, 1185.
21. Weygand, F.; Trauth, O., *Chem. Ber.* **1952**, *85*, 57.
22. Angibeaud, P.; Utille, J.-P., *J. Chem. Soc. Perkin Trans. I* **1990**, 1490.
23. Miethchen, R.; Holz, J.; Peters, D.: *Z. Chem.* **1989**, *9*, 420.