J. prakt. Chem. 337 (1995) 189–195

Journal für praktische Chemie
Chemiker-Zeitung

Organofluorine Compounds and Fluorinating Agents. 14 [1]

Thermotropic Liquid-Crystalline Glycosyl Fluorides

Ralf Miethchen and Cornelia Zur

Rostock, Department of Organic Chemistry, University

Received September 5th, 1994 respectively November 11th, 1994

Abstract. The liquid crystalline 6-O-alkyl-α-D-galactopyranosyl fluorides (**3a–f**) and the mesogenic 6-O-dodecyl-α-D-glucopyranosyl fluoride (**7**) were prepared from the homologous 6-O-alkyl-1,2:3,4-di-O-isopropylidene-α-D-galactopyranosides (**1a–f**) and from the methyl 2,3,4-tri-O-benzyl-glucopyranoside (**4**), respectively, in two and three steps. The fluorinations of **1a–f** to the α-fluorides **2a–f** and of **5** to the α-fluoride **6** were carried out with the reagent system HF/nitromethane/acetic anhydride, which simultaneously effects the complete exchange of the isopropylidene groups (**1a–f**) and of the benzyl groups (**5**) for acetyl functions in the non-glycosidic positions. Moreover, the 6-O-dodecyl-2,3,4-tri-O-acetyl-β-D-galactopyranosyl fluoride (**11**) was prepared in three steps from the 6-O-dodecyl-galactopyranose (**8**). The stereoselective introduction of the fluoride into the β-anomeric position (**10** → **11**) was achieved by bromide-fluoride exchange with the two-phase system triethylamine-trishydrofluoride/petroleum ether. Dodecyl 6-deoxy-6-fluoro-α-D-glucopyranoside (**13**), prepared from the glucoside **12** with the fluorinating agent DAST, shows a narrow monotropic S_A-phase and lyotropic liquid crystalline behaviour in contact with water. Dodecyl 6-deoxy-6-fluoro-β-D-galactopyranoside (**17**), prepared in three steps from the acetal **14**, does not form mesophases. The liquid crystalline behaviour of the amphiphilic glycosyl fluorides **3a–f**, **7**, and of the 6-deoxy-6-fluoro derivative **13** is described.

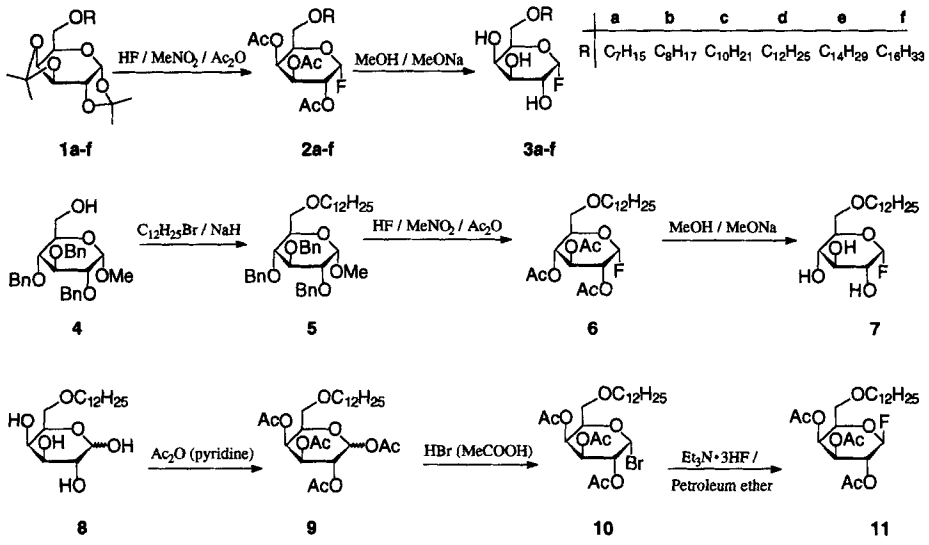
Amphiphilic carbohydrate derivatives are interesting because of their biological importance [2], their surfactant properties [3, 4], and increasingly for their liquid crystalline behaviour for some years [5, 6]. Recently, the first liquid crystalline fluorinated carbohydrates (4,6-O-alkylidene-2-deoxy-2-fluoro-D-glucopyranoses [7] and alkyl 2-deoxy-2-fluoro-D-glucopyranosides [1b]) were described. Previous systematic studies of various "single tailed" amphiphilic D-glucopyranoses [6, 8] and D-galactopyranoses [9, 10] had shown that their thermal behaviour significantly depends on the site of substitution of the lipophilic chain. On the other hand, it was observed that in the case of fluoro-deoxy derivatives the site of the OH for F substitution has a decisive influence on the thermal properties, i.e. the range of the mesophases is significantly reduced or the liquid crystalline properties are entirely lost [7, 10]. Only in the case of the alkyl 2-deoxy-2-fluoro-β-D-glucopyranosides was a destabilisation of the mesophases not found [1b].

We turned our further attention to the synthesis of liquid crystalline glycosyl fluorides. Such mesogens could be glycosyl donors for selective thermal glycosylations with mesogenic sugars using the ordered supramolecular structures of smectic mesophases.

Results and Discussion

Synthesis

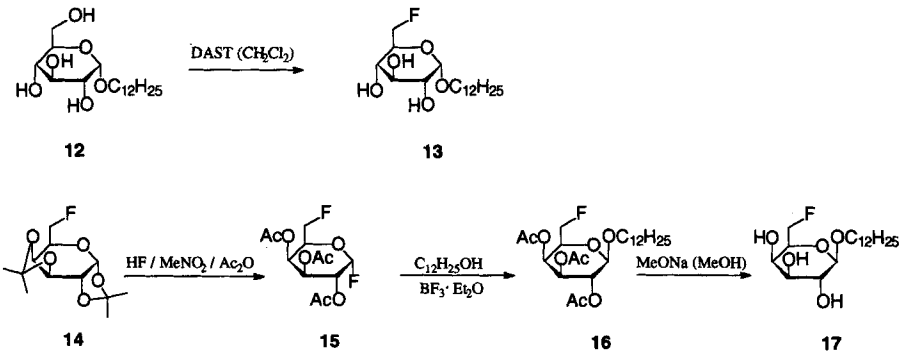
At first we prepared the homologous series of 6-O-alkyl-α-D-galactopyranosyl fluorides **3a–f** as well as the 6-O-dodecyl-α-D-glucopyranosyl fluoride (**7**) according to scheme 1, because the evaluation of the thermal behaviour of all the fluorine-free [6, 8, 9] and fluorine-containing [1b, 7] "single tailed" D-glucopyranoses and D-galactopyranoses allowed to predict that fluorides with this arrangement of the lipophilic chain are the most likely to form mesophases. To synthesize the α-D-galactopyranosyl fluorides **3a–f** the homologous 6-O-alkyl-1,2:3,4-di-O-isopropylidene-α-D-galactopyranoses **1a–f** [9, 11, 12] were exclusively transformed to the thermodynamically favoured α-fluorides **2a–f** using the system HF/nitromethane/acetic anhydride [13]. This reaction simultaneously effects an acetal cleavage and the acetylation of all non-glycosidic positions. Because the acetylation step is very fast, no ring contraction took place [14]. Zemplén-deacetylation [15] of the fluorides **2a–f** with methanolic sodium methanolate gave the amphiphilic galactosyl fluorides **3a–f** in good yields (scheme 1).



The 6-O-dodecyl-α-D-glucopyranosyl fluoride (**7**) was synthesized from methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside (**4**) [16] in three steps. The O-alkylation of **4** to the 6-O-alkyl-derivative **5** was carried out with dodecyl bromide and NaH in anhydrous DMF with reference to previously reported procedures [9, 11, 12]. The subsequent introduction of the anomeric fluoride into **5** was carried out with the system HF/nitromethane/acetic anhydride yielding exclusively the α-glucosyl fluoride **6**. However, it should be noticed that this reaction is accompanied by a complete exchange of all three benzyl groups by acetyl functions under the applied reaction conditions (15 h at r.t.). The deprotection of the fluoride **6** can be effected by methanolic sodium methanolate (scheme 1).

Furthermore, an β-anomeric fluoride was prepared in order to check its reactivity in comparison to the α-isomers. To this end, 6-O-dodecyl-D-galactopyranose (**8**) was peracetylated with acetic anhydride in pyridine, the resulting derivative **9** was transformed to the α-bromide **10** by treatment with the hydrobromic acid/acetic acid reagent mixture [17]. The bromide for fluoride exchange to prepare the β-fluoride **11** was carried out by refluxing **10** in the two-phase system of triethylamine-trishydrofluoride/petroleum ether (scheme 1). This procedure, which is based upon the kinetically controlled introduction of fluoride, was commented by us more detailed in a previous paper [18]. The cautious deacetylation of **11**, carried out under Zemplén-conditions, gave a mixture of the 6-O-dodecyl-β-D-galactopyranosyl fluoride and relatively large amounts of the methyl 6-O-dodecyl-α-D-galactopyranoside. We relinquished on a chromatographic separation of the very unstable β-fluoride.

Furthermore, the dodecyl 6-deoxy-6-fluoro-α-D-glucopyranoside (**13**) and the dodecyl 6-deoxy-6-fluoro-β-D-galactopyranoside (**17**) were prepared (scheme 2). In these compounds the sites of substitution of fluoride and of the alkyl chain are exchanged compared to the glycosyl fluorides **3d** and **7** (scheme 1). The treatment of the glucoside **12** [6, 19] with DAST (diethylaminosulfurtrifluoride) at r.t. in dichloromethane (for analogeous procedures see ref. [20]) gave dodecyl 6-deoxy-6-fluoro-α-D-glucopyranoside (**13**) in a yield of 31 % (no optimized reaction). The β-galactoside **17** was prepared in a 3-step synthesis from 6-deoxy-6-fluoro-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (**14**) [21]. The transformation of **14** to the difluoro derivative **15** was accomplished by the reagent system HF/nitromethane/acetic anhydride at r.t. (15 h). The obtained glycosyl donor **15** reacted with dodecan-1-ol in acetonitrile (0 °C) under BF_3-catalysis (analogeous procedures see



ref. [22]) to give the β-galactoside **16**. The latter was deacetylated by methanolic sodium methanolate to the target product **17**.

Structure and Stereochemistry

The structure and stereochemistry of the compounds **2a–f, 3a–f, 6, 7, 11, 13, 15–17** were supported by ^{1}H-, ^{13}C-, and ^{19}F-NMR spectroscopy. The structure-determinating data are summarized in the experimental part. Because of the similarity of the spectra of homologous series (**2a–f, 3a–f**), only one representative spectrum of each series is presented. The chemical shifts and the coupling constants of all described D-gluco- and D-galactopyranose derivatives are comparable to the corresponding data of structural similar derivatives reported in literature (reviews [23, 24]). From the spectra can be concluded that the compounds exist as pure isomers in all cases. All α-configured derivatives **2, 3, 6, 7, 13, 15** give small H-1/H-2-coupling constants because they have an equatorial (H-1) to axial (H-2) arrangement. The measured $J_{1/2}$-values for the compounds **2, 3, 6, 7, 13, 15** are about 2.7 Hz confirming the α-configuration. In addition, the coupling constants of fluorine with the neighbouring H- and C-atoms (**3c**: $J_{H-1/F} \approx 54.6$ Hz / $J_{C-1/F} \approx 223.4$ Hz; **7**: $J_{H-1/F} \approx 54.0$ Hz / $J_{C-1/F} \approx 224.4$ Hz, $J_{C-2/F} \approx 24.9$ Hz) are characteristic for α-fluorides (see ref. [23]). The corresponding chemical shifts of H-1 and C-1 of the α-fluorides **3** and **7** are δ = 5.53/109.1 and δ = 5.50/108.7, respectively.

The $J_{1/2}$-values of ≈ 7.0 Hz for the fluoride **11** and of ≈ 7.9 Hz and of ≈ 7.6 Hz, respectively, for the galactosides **16** and **17** are characteristic for a diaxial arrangement of H-1 and H-2 proving the β-configuration at the anomeric centre. Furthermore, the chemical shifts of **11** (H-1, δ = 5.22 and C-1, δ = 107.2) as like as the couplings $J_{H-1/F} \approx 49.1$ Hz, $J_{H-2/F} \approx 10.7$ Hz, $J_{C-1/F} \approx 217.3$ Hz, $J_{C-2/F} \approx 24.8$ Hz, and $J_{C-3/F} \approx 11.3$ Hz additionally support this conclusion.

Finally, the chemical shift of the protons in 6-position of compound **13** (δ = 4.57) and the coupling of the F-atom with H-6/H-6′ (47.9 Hz) confirm the successful introduction of fluorine in this position by DAST. Furthermore, all fluorine derivatives described here show the expected peaks in the ^{19}F-NMR spectra.

Thermal behaviour

The interactions of amphiphilic carbohydrates within a mesophase are composed of two different contributions, namely the hydrogen bonds between the OH-groups of the hydrophilic head groups and the van der Waals interactions among the alkyl chains. By a revised model recently reported by Jeffrey [5d] and van Doren [25] the thermal behaviour of smectic liquid crystals based on amphiphilic carbohydrates can be described. On heating, at first the rupture from the crystal lattice to the molecular clusters takes place between hydrogen-bonded head groups. The lipophilic chains of the amphiphils form the core of the smectic bilayer whereas the carbohydrate moieties are arranged on the outside of the layers. Consequently, amphiphilic sugars such as "single-tailed" monosaccharides show a higher sensitivity to thermal motion of hydrogen-bonding compared to the alkyl chain packing [5d, 25].

The relative arrangement of the OH-groups in the self-assembled supramolecular structures of "single tailed" amphiphils depends on bonding site of the lipophilic chain to the head group (dissimilar packing of the head groups within the bilayer). Consequently, amphiphilic monosaccharides with different sites of the alkyl chain form a more or less effective hydrogen bonding network, i.e. the interactions between neighbouring bilayers as well as the interactions within a bilayer may strongly vary. The introduction of fluorine (being at best a H-bonding acceptor, no donor) replacing a hydroxyl group (H-bonding donor and -acceptor) leads to defects in the H-bonding network, reducing the stability of the mesophase.

On heating, the homologous 6-O-alkyl-α-D-galactopyranosides **3a–f** form smectic S_A phases, however, a slow HF elimination (bubble formation) is already observed at temperatures slightly above the melting point of the compounds, i.e. mixtures of different components are created during the heating. These mixtures likewise show liquid crystalline behaviour (S_A). Their clearing points, determined by polarizing microscopy, were reproducible (figure 1). We could not identify any individual component of the mixtures. Consequently, we do still not know glycosylations (intermolecular HF elimination) occur or an intramolecular HF elimination followed by oligomerisations is taking place.

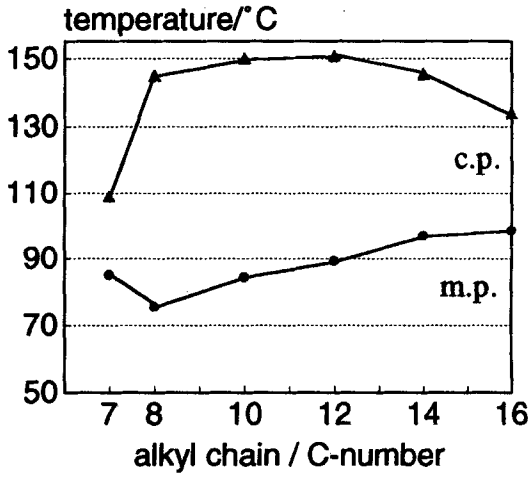


Fig. 1 Thermal behaviour of the 6-O-alkyl-α-D-galactopyranosyl fluorides **3a–f**

The galactosyl fluorides **3a–f** melt about 20–30 K lower than the corresponding fluorine-free 6-O-alkyl-D-galactopyranoses [9]. Thus, 6-O-dodecyl-D-galactopyranose (**8**) [9] melts at 122–123 °C and clears at 168 °C [9b], whereas the fluoride **3d** melts at 88–89 °C. The clearing points are not directly comparable because of the HF-elimination.

The 6-O-dodecyl-α-D-glucopyranosyl fluoride (**7**) melts at 80.5–81.5 °C forming a smectic S_A phase. The start of the HF-elimination was observed at 83 °C. The resulting mesogenic mixture shows the wide clearing range of 126.5–136.5 °C, which additionally depends on the heating rate. The fluorine-free 6-O-dodecyl-D-glucopyranose melts at 92–94 °C and clears at 163 °C [8]. Consequently, in each case a decrease of the melting points of **3a–f** and **7** is observed compared to the melting points of the corresponding fluorine-free OH-containing compounds.

Both the dodecyl 6-deoxy-6-fluoro-glycopyranosides **13** and **17**, respectively, do not form enantiotropic mesophases. The derivative **13** shows only monotropic and lyotropic (in contact with water) properties. This result was not unexpected because various alkyl 6-deoxy-glycosides do not show liquid crystalline behaviour as well [26]. The fluorine atom is bonded to a flexible exocyclic side chain. That should make its inclusion as H-acceptor to the H-bonding network more difficult. Consequently, the structural situation of the 6-deoxy-6-fluoro-derivatives **13** and **17** is similar to the amphiphilic fluorine-free 6-deoxy derivatives described in ref. [26]. In contrast to the fluoro-derivative **17** the dodecyl β-D-galactopyranoside [6] as well as the dodecyl α-D-galactopyranoside [27] shows liquid crystalline behaviour.

The authors are grateful to Dr. Heiko Prade for his kind cooperation. Furthermore, we thank the "Deutsche Forschungsgemeinschaft", the "Herbert Quandt-Stiftung", and the "Fonds der Chemischen Industrie" for financial support of our research.

Experimental

Column chromatography (Silica Gel 60, 0.063–0.2 mm, Merck) and thin layer chromatography (Silica Gel 60 foils F_{254}, Merck). ^{1}H-, ^{13}C-, ^{19}F-NMR: Bruker AC 250. Textural observations and measurements of melting (m.p.) and clearing points (c.p.) were carried out with a Leitz Laborlux 12 Pol polarising microscope equipped with a Mettler FP 90 hot stage. The solvent "petroleum ether" used for the quenching of some reaction mixtures was a fraction boiling at 60–85 °C.

6-O-Alkyl-α-D-galactopyranosyl fluorides (3a–f)

a) 2,3,4-Tetra-O-acetyl-6-O-alkyl-α-D-galactopyranosyl fluorides (**2a–f**)

To a solution of 5 mmol of the corresponding 6-O-alkyl-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose **1a** [9], **1b** [9, 12], **1c** [9, 12], **1d** [9, 11], **1e** [9, 11], **1f** [9] in 15 ml of nitromethane and 3 ml of acetic anhydride 4 ml (0.2 mol) of anhydrous HF were added at 0 °C (HF-resistant equipment!) and the closed vessel was allowed to stand at r.t. for 15 h. Then, the reaction mixture was carefully poured into a cooled solution of 20 ml (0.15 mol) of Et_3N in 200 ml of petroleum ether. The polar phase was separated and extracted with 100 ml of the petroleum ether once more. The combined hydrocarbon phases were washed with saturated aqueous $NaHSO_4$ (50 ml), 50 ml of water, dried (Na_2SO_4), and concentrated under reduced pressure to give syrups which on column chromatographic separation (eluent: toluene/ ethyl acetate 10 : 1 v/v; R_f = 0.31–0.43) yielded colourless syrups of **2a–f** (45–88 %).

2a: $C_{19}H_{31}O_8F$ (406.45) calcd. C 56.15, H 7.69, found C 56.52, H 7.63

2b: $C_{20}H_{33}O_8F$ (420.48) calcd. C 57.13, H 7.91, found C 57.25, H 8.14, (see also ref. [13])

2c: $C_{22}H_{37}O_8F$ (448.53) calcd. C 58.91, H 8.31, found C 58.93, H 8.14, (see also ref. [13])

2d: $C_{24}H_{41}O_8F$ (476.58) calcd. C 60.49, H 8.67, found C 60.54, H 8.63, (see also ref. [11])

2e: $C_{26}H_{45}O_8F$ (504.64) calcd. C 61.88, H 8.99, found C 61.84, H 8.85, (see also ref. [11])

2f: $C_{28}H_{49}O_8F$ (532.69) calcd. C 63.13, H 9.27, found C 63.30, H 9.50

2c[1]: ^{1}H-NMR (250 MHz / $CDCl_3$ / TMS): δ = 0.86 (t, 3H, CH_3), 1.20–1.28 (m, 14H, CH_2), 1.50 (m, 2H, CH_2-β), 1.96, 2.08, 2.11 (3s, 3 × 3H, 3Ac), 3.36 (m, 3H, H-6', CH_2-α), 3.51 (dd, 1H, $J_{6/6'}$ = 10.0, H-6), 4.30 (ddd, 1H, $J_{5/6}$ = 6.1, $J_{5/6'}$ = 6.1, H-5), 5.15 (ddd, 1H, $J_{2/3}$ = 10.7, $J_{2/F}$ = 23.5, H-2), 5.34 (dd, 1H, $J_{3/4}$ = 3.3, H-3), 5.52 (dd, 1H, $J_{4/5}$ = 1.5, H-4), 5.77 (dd, 1H, $J_{1/2}$ = 2.7, $J_{1/F}$= 53.7, H-1). – ^{13}C-NMR (62 MHz / $CDCl_3$ / TMS): δ = 14.0 (CH_3), 20.5, 20.5, 20.6 (OCO*C*H_3), 22.6–31.9 (CH_2), 67.2 (C-3), 67.7 (d, $J_{C-2/F}$ = 24.1, C-2), 68.0 (C-4), 68.3 (C-6), 69.9 (d, $J_{C-5/F}$ = 3.4, C-5), 71.9 (CH_2-α), 104.4 (d, $J_{C-1/F}$ = 227.8, C-1), 169.8, 169.8, 170.2 (O*C*OCH$_3$). – ^{19}F-NMR (235 MHz / $CDCl_3$ / $CFCl_3$): δ_F = –150.2.

b) 6-O-Alkyl-α-D-galactopyranosyl fluorides (**3a–f**)

0.3 mmol of the corresponding fluorides **2a–f** were similarly deacetylated as described by Zemplén [15]; for the long-chain derivatives complete solubility is achieved by adding of small amounts of ethyl acetate or acetone. The reaction is finished within 30 min. (t.l.c.-control; eluent: dichloromethane/methanol 6 : 1 v/v; R_f: 0.37–0.46). After cautious neutralisation with an acidic ion exchange residue (Lewatit S) the solution was filtrated, concentrated under reduced pressure, and the crystalline colourless residues were recrystallized from hexane. Yield 57–95 %.

3a: Yield 71.6 mg (85.3 %); m.p. 84–85 °C; c.p.: 107-109 °C, $C_{13}H_{25}O_5F$ (280.34) calcd. C 55.70, H 8.99, found C 55.46, H 8.99

3b: Yield 70.6 mg (80.1 %); m.p. 75–75.5 °C, c.p. 142.5–145 °C, $C_{14}H_{27}O_5F$ (294.36) calcd. C 57.12, H 9.24, found C 56.99, H 9.15

[1] Deviations within the homologous series of **2a–f**: ^{1}H-NMR ± 0.05 ppm/± 0.2 Hz; ^{13}C-NMR ± 0.01ppm/± 0.1 Hz; ^{19}F-NMR ± 0.05 ppm

3c: Yield 84.6 mg (87.6 %), m.p. 84–84,5 °C, c.p. 146–150 °C, $C_{16}H_{31}O_5F$ (322.42) calcd. C 59.61, H 9.69, found C 57.94, H 9.92

3d: Yield 99.3 mg (94.6 %), m.p. 88–89 °C, c.p. 146.5–151 °C, $C_{18}H_{35}O_5F$ (350.47) calcd. C 61.69, H 10.07, found C 61.30, H 10.16

3e: Yield 72.0 mg (63.5 %), m.p. 97 °C, c.p. 142.5–145.5 °C, $C_{20}H_{39}O_5F$ (378.53) calcd. C 63.46, H 10.38, found C 62.91, H 10.47

3f: Yield 69.2 mg (56.8 %), m.p. 97.5–99 °C, c.p. 134 °C, $C_{22}H_{43}O_5F$ (406.58) calcd. C 64.99, H 10.66, found C 64.93, H 10.66

3c[2]: ^{1}H-NMR (250 MHz / acetone-d_6 / TMS): δ = 0.86 (t, 3H, CH_3), 1.20–1.37 (m, 14H, CH_2), 1.52 (m, 2H, CH_2-β), 3.43 (m, 2H, H-5, 1 CH_2-α), 3.55 (dd, 1H, $J_{5/6}$ = 6.4, $J_{6/6'}$ = 10.1, H-6), 3.66 (dd, 1H, $J_{5/6'}$ = 5.5, H-6'), 3.80 (m, 3H, H-2, OH, 1 CH_2-α), 4.03 (m, 4H, H-3, H-4, 2 OH), 5.53 (dd, 1H, $J_{1/2}$ = 2.7, $J_{1/F}$ = 54.6, H-1).

3b: ^{13}C-NMR (62 MHz / acetone-d_6 / TMS) δ = 14.3 (CH_3), 23.3–32.6 (CH_2), 69.7 (d, $J_{C-2/F}$ = 24.7, C-2), 70.1 (C-4), 70.6 (CH_2-α), 70.7 (C-3) , 72.0 (C-6), 72.7 (d, $J_{C-5/F}$ = 3.0, C-5), 109.1 (d, $J_{C-1/F}$ = 223.4, C-1). – ^{19}F-NMR (235 MHz / $CDCl_3$ / $CFCl_3$): δ_F = –152.6.

6-O-Dodecyl-α-D-glucopyranosyl fluoride (7)

a) Methyl 2,3,4-tri-O-benzyl-6-O-dodecyl-α-D-glucopyranoside (**5**)

To a solution of 9.28 g (20 mmol) of methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside (**4**) [16] in 100 ml of anhydrous DMF 2.8 g of NaH (80 %-emulsion in paraffin oil) were added in small portions at 0 °C under stirring. After further 10 min. the mixture was allowed to warm up to r.t. and 5.48 g (22 mmol) of dodecyl bromide were added. The suspension was stirred for 2 h, the unreacted NaH was carefully decomposed by adding 100 ml of water, and the aqueous solution was extracted with petroleum ether (3 · 75 ml). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure to give a syrup (11.9 g) still containing small parts of unreacted alkylbromide (t.l.c.: dichloromethane/acetone 95 : 5 v/v;. R_f : 0.75–0.82). This product was used for the synthesis of **6** without further purification (crude yield: 90 %).

b) 2,3,4-Tri-O-acetyl-6-O-dodecyl-α-D-glucopyranosyl fluoride (**6**)

3.2 g (5 mmol) of **5** were fluorinated as described for **3a–f** (15 ml of nitromethane/3 ml of acetic anhydride/6 ml (0.3 mol) of HF) and the mixture was worked up analogously. Purification of the obtained colourless syrup by column chromatography (eluent: toluene/ethyl acetate 15 : 1 v/v; R_f = 0.32) yielded 84 mg (36 %) of **6** as a syrup.

$C_{24}H_{41}O_8F$ (476.58) calcd. C 60.49, H 8.67, found C 60.98, H 8.71

^{1}H-NMR (250 MHz / $CDCl_3$ / TMS): δ = 0.87 (t, 3H, CH_3), 1.20–1.35 (m, 18H, CH_2), 1.53 (m, 2H, CH_2-β), 2.01, 2.02, 2.09 (3s, 3 · 3H, 3Ac), 3.42 (m, 3H, H-6', 2 CH_2-α), 3.56 (dd, 1H, $J_{5/6}$ = 2.7, $J_{6/6'}$ = 11.3, H-6), 4.10 (ddd, 1H, $J_{5/6'}$ = 3.0, $J_{4/5}$ = 9.5, H-5), 4.93 (ddd, 1H, $J_{1/2}$ = 2.7, $J_{2/3}$ = 10.1, $J_{2/F}$ = 24.1, H-2), 5.17 (dd, 1H, $J_{3/4}$ = 9.8, H-4), 5.47 (dd, 1H, H-3), 5.73 (dd, $J_{1/F}$ = 53.1, H-1);

^{13}C-NMR (62 MHz / $CDCl_3$ / TMS): δ = 14.0 (CH_3), 20.6, 20.5, 20.4 ($OCOCH_3$), 22.6-31.9 (CH_2), 68.2, 69.7 (C-3, C-4), 68.7 (C-6), 70.4 (d, $J_{C-2/F}$ = 24.6, C-2), 71.0 (d, $J_{C-5/F}$ = 3.9, C-5), 72.1 (CH_2-α), 103.8 (d, $J_{C-1/F}$ = 228.8, C-1), 169.3, 169.9, 170.0 ($OCOCH_3$). – ^{19}F-NMR (235 MHz / $CDCl_3$ / $CFCl_3$): δ_F = –149.4.

c) 6-O-Dodecyl-α-D-glucopyranosyl fluoride (**7**)

143 mg (0.3 mmol) of **6** were deacetylated as described for **3a–f** yielding colourless crystals of **7** (80 mg; 75.8 %), which were recrystallized from hexane; t.l.c.: dichloromethane/methanol 6:1 v/v; R_f = 0.61.

m.p. 80.5–81.5 °C, c.p. 126.5-136.5 °C (accompanied by decomposition)

$C_{18}H_{35}O_5F$ (350.47) calcd. C 61.69, H 10.07, found C 61.60, H 10.09

^{1}H-NMR (250 MHz / acetone-d_6 / TMS): δ = 0.86 (t, 3H, CH_3), 1.20–1.35 (m, 18H, CH_2), 1.53 (m, 2H, CH_2-β), 3.42 (m, 4H, H-2, H-4, CH_2-α), 3.63 (m, 3H, H-6, H-6', OH), 3.76 (ddd, 1H, $J_{4/5}$ = 10.1, $J_{5/6}$ = 5.2, $J_{5/6}$ = 2.4, H-5), 4.20 (m, 3H, H-3, 2 OH), 5.50 (dd, 1H, $J_{1/2}$ = 2.7, $J_{1/F}$ = 54.0, H-1). – ^{13}C-NMR (62 MHz / acetone-d_6 / TMS): δ = 14.3 (CH_3), 23.3–32.6 (CH_2), 70.7 (C-4), 70.8 (C-6), 72.2 (C-3), 73.0 (d, $J_{C-2/F}$ = 24.9, C-2), 74.5 (CH_2-α), 74.9 (d, $J_{C-5/F}$ = 3.6, C-5), 108.7 (d, $J_{C-1/F}$ = 224.4, C-1). – ^{19}F-NMR (235 MHz / acetone-d_6 / $CFCl_3$): δ_F = –150.6, $J_{1/F}$ = 54.0 Hz, $J_{2/F}$ = 23.3 Hz.

2,3,4-Tri-O-acetyl-6-O-dodecyl-β-D-galactopyranosyl fluoride (11)

a) 1,2,3,4-Tetra-O-acetyl-6-O-dodecyl-D-galactopyranose (**9**)

To a solution of 4.83 g (13.9 mmol) of 6-O-dodecyl-D-galactopyranose (**8**) [9] in 20 ml of anhydrous pyridine 20 ml of acetic anhydride were added at 0 °C and the mixture was allowed to stand overnight. Then the solution was concentrated under reduced pressure, the residue dissolved in 100 ml of chloroform (t.l.c.: toluene/ethyl acetate 6 : 1 v/v; R_f = 0.38) and the solution washed with 50 ml of water, 50 ml of aqueous $NaHCO_3$ and with 50 ml of water. After drying (Na_2SO_4) and evaporation of the organic solvent, the syrupy residue was used to prepare the bromide **10** without further purification; yield of **9**: 3.79 g (52.8 %).

b) 2,3,4-Tri-O-acetyl-6-O-dodecyl-α-D-galactopyranosyl bromide (**10**)

To a solution of 1.0 g (1.94 mmol) of **9**, dissolved in 12 ml of dichloromethane, 2.8 ml of the brominating agent (40 % HBr in acetic acid, w /w) were added. The mixture was stirred for 30–45 min at r.t., diluted with 50 ml of dichloromethane and poured into 100 ml of ice-water. The organic phase was washed with 20 ml of cold saturated aqueous $NaHSO_4$, dried (Na_2SO_4) and concentrated. The instable bromide **10** (0.91 g/ 87 %, syrup) was used for the following procedure without any purification (t.l.c. of **10**: toluene/ethyl acetate 6 : 1 v/v; R_f: 0.55).

---

[2] Deviations within the homologous series of **3a–e**: ^{1}H-NMR ± 0.05 ppm/± 0.3 Hz; ^{13}C-NMR ± 0.1 ppm/± 0.4 Hz; ^{19}F-NMR ± 0.1 ppm; **3f** is insufficiently soluble in acetone

c) 2,3,4-Tri-O-acetyl-6-O-dodecyl-β-D-galactopyranosyl fluoride (**11**)

1.1 g (2 mmol) of **10**, dissolved in ca. 5 ml of $CHCl_3$, were added to the two-phase system petroleum ether/ triethylamine-trishydrofluoride (prepared from 50 ml of petroleum ether, 7 ml (50 mmol) of anhydrous Et_3N and 3 ml (150 mmol) of anhydrous HF at –20 °C) [18] and the mixture was refluxed for 20 h. After this time ca. 90 % of the starting material had vanished. After phase separation the triethylamine-trishydrofluoride phase was extracted with 20 ml of petroleum ether. The combined hydrocarbon phases were washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: toluene/ethyl acetate 15 : 1 v/v; R_f: 0.25) yielding **11** as a colourless syrup; 0.86 g (90 %).

$C_{24}H_{41}O_8F$ (476.58) calcd. C 60.49, H 8.67, found C 60.37, H 8.50

^{1}H-NMR (250 MHz / $CDCl_3$ / TMS): δ = 0.86 (t, 3H, CH_3), 1.20–1.31 (m, 18H, CH_2), 1.50 (m, 2H, CH_2-β), 1.97, 2.07 , 2.13 (3s, 3 · 3H, 3Ac), 3.41 (m, 3H, H-6, CH_2-α), 3.57 (dd, 1H, $J_{5/6}$ = 6.1, $J_{6/6'}$ = 10.1, H-6'), 3.91 (ddd, 1H, $J_{4/5}$ = 1.5, $J_{5/6}$ = 6.4, H-5), 5.02 (dd, 1H, $J_{3/4}$ = 3.4, $J_{2/3}$ = 10.4, H-3), 5.22 (dd, 1H, $J_{1/2}$ = 7.0, $J_{1/F}$ = 49.1, H-1), 5.26 (ddd, 1H, $J_{2/F}$ = 10.7, H-2), 5.42 (dd, 1H, H-4). – ^{13}C-NMR (62 MHz / $CDCl_3$ / TMS): δ = 14.0 (CH_3), 20.4, 20.5, 20.6 (OCO*C*H_3), 22.6–31.9 (CH_2), 67.0 (C-4), 68.2 (C-6), 69.1 (d, $J_{C-2/F}$ = 24.8, C-2), 70.2 (d, $J_{C-3/F}$ = 11.3, C-3), 72.0 (CH_2-α), 72.5 (d, $J_{C-5/F}$ = 4.6, C-5), 107.2 (d, $J_{C-1/F}$ = 217.3, C-1), 169.9, 169.9, 169.2 (O*C*OCH$_3$). – ^{19}F-NMR (235 MHz / $CDCl_3$ / CFCl3): δ_F = –141.4.

Dodecyl 6-deoxy-6-fluoro-α-D-glucopyranoside (**13**)

To a stirred and cooled (–40 °C) suspension of 0.4 g (1.15 mmol) of dodecyl α-D-glucopyranoside (**12**) [6, 19] in 5 ml of anhydrous CH_2Cl_2 0.9 ml (6.9 mmol) of DAST were added and the mixture was allowed to warm up to r.t.. The reaction was finished within 45 min. After quenching by 2.5 ml of methanol at –10 °C, the solution was concentrated under reduced pressure and purified by column chromatography (eluent: ethyl acetate; R_f : 0.35). Yield of **13**: 124.7 mg (31 %).

m.p. 52.5 °C, c.p. 44.5 °C (monotropic), c.p. (lyotropic phase, water): 132 °C

$C_{18}H_{35}O_5F$ (350.47) calcd. C 61.69, H 10.07 found C 61.92, H 9.99

^{1}H-NMR (250 MHz / acetone-d_6 / TMS): δ = 0.86 (t, 3H, CH_3), 1.23–1.40 (m, 18H, CH_2), 1.56 (m, 2H, CH_2-β), 3.36 (m, 4H, H-2, H-3, H-4, 1 CH_2-α), 3.68 (m, 3H, H-1, H-5, 1 CH_2-α), 3.97 (d, 1H, OH), 4.19 (d, 1H, OH), 4.57 (m, 2H, $J_{6/F}$ = $J_{6'/F}$ = 47.9, H-6, H-6'), 4.75 (d, 1H, OH). – ^{13}C-NMR (62 MHz / DMSO-d_6 / TMS): δ = 14.0 (CH_3), 22.3–31.5 (CH_2), 67.4 (CH_2-α), 69.2 (d, $J_{C-4/F}$ = 6.8, C-4), 71.0 (d, $J_{C-5/F}$ = 17.4, C-5), 71.9 (C-2), 73.3 (C-3), 82.9 (d, $J_{C-6/F}$ = 169.2, C-6), 98.9 (C-1). – ^{19}F-NMR (235 MHz / DMSO-d_6 / $CFCl_3$): δ_F = –231.9.

Dodecyl 6-deoxy-6-fluoro-β-D-galactopyranoside (**17**)

a) 2,3,4-Tri-O-acetyl-6-deoxy-6-fluoro-α-D-galactopyranosyl fluoride (**15**)

0.87 g (3.3 mmol) of 6-deoxy-6-fluoro-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (**14**) [21] were fluorinated to **15** in the system nitromethane(2 ml) / acetic anhydride(1 ml) / anhydrous HF (1 ml) as described for the compounds **2a–f**. After cautious quenching in $CHCl_3$ (100 ml)/Et_3N (8 ml) the reaction mixture was worked up as described for **2a–f** and the crude product purified by column chromatography (eluent: toluene/ethyl acetate 6 : 1 v/v; R_f = 0.31); the obtained syrup solidified in the refrigerator; yield: 0.45 g (51.8 %).

15: ^{1}H-NMR (250 MHz / $CDCl_3$ / TMS): δ = 1.94, 2.05, 2.08 (3s, 3 · 3H, 3Ac), 4.36 (ddd, 1H, $J_{5/6}$ = 3.7, $J_{6/6'}$ = 9.2, $J_{6/F-6}$ = 42.4, H-6), 4.36 (m, 1H, H-5), 4.43 (ddd, 1H, $J_{5/6}$ = 6.1, $J_{6'/F-6}$ = 42.4, H-6'), 5.13 (ddd, 1H, $J_{1/2}$ = 2.7, $J_{2/3}$ = 11.0, $J_{2/F-1}$ = 23.5, H-2), 5.31 (dd, 1H, $J_{3/4}$ = 3.3, H-3), 5.51 (dd, $J_{4/5}$ = 1.2, H-4), 5.75 (dd, $J_{1/F-1}$ = 53.4, H-1). – ^{13}C-NMR (62 MHz / $CDCl_3$ / TMS): δ = 20.4, 20.5, 20.5 (OCO*C*H_3), 66.9 (C-3), 67.3 (d, $J_{C-4/F-6}$ = 5.2, C-4), 67.4 (d, $J_{C-2/F-1}$ = 24.0, C-2), 69.4 (dd, $J_{C-5/F-1}$ = 3.8, $J_{C-5/F-6}$ = 23.8, C-5), 80.6 (d, $J_{C-6/F-6}$ = 172.6, C-6), 104.3 (d, $J_{C-1/F-1}$ = 228.9, C-1), 169.7, 169.8, 170.2 (O*C*OCH$_3$). – ^{19}F-NMR (235 MHz / $CDCl_3$ / $CFCl_3$): δ = –150.7 (dd, $J_{1/F-1}$ = 53.2, $J_{2/F-1}$ = 23.3, F-1), –232.1 (ddd, $J_{5/F-6}$ = 15.2, $J_{6/F}$ = $J_{6'/F}$ = 45.8, F-6).

b) Dodecyl 2,3,4-tri-O-acetyl-6-deoxy-6-fluoro-β-D-galactopyranoside (**16**)

0.5 g (1.9 mmol) of **15** and 0.53 ml (2.3 mmol) of dodecan-1-ol were dissolved in 5 ml of anhydrous acetonitrile and a small amount of powdered and activated molecular sieves (3 Å) was added. The mixture was stirred for 10 min at r.t., cooled down to 0 °C, 0.33 ml (2.7 mmol) of BF_3-etherate was added and the reaction continued for 1 h at 0 °C (t.l.c.-control). Then, the molecular sieves were filtered off using Silica Gel, the filtrate diluted with 20 ml of CH_2Cl_2, washed with 10 ml of saturated aqueous $NaHSO_4$, dried (Na_2SO_4) and concentrated. The β-anomeric product **16**, still containing small parts of dodecanol after the column chromatographic separation (eluent: toluene/ethyl acetate 15 : 1 v/v; R_f: 0.21; yield 0.76 g (84.5 %)), was directly deacetylated to **17**.

16: ^{1}H- NMR (250 MHz / $CDCl_3$ / TMS): δ = 0.81 (t, 3H, CH_3), 1.10–1.35 (m, 18 H, CH_2), 1.49 (m, 2 H, CH_2-β), 1.91, 1.97, 2.07 (3s, 3 · 3H, 3Ac), 3.41 (m, 1H, CH_2-α), 3.86 (m, 2H, H-5, CH_2-α), 4.34 (ddd, 1H, $J_{5/6}$ = 5.5, $J_{6/6'}$ = 9.8, $J_{6/F}$ = 46.7, H-6), 4.41 (d, 1H, $J_{1/2}$ = 7.9, H-1), 4.42 (ddd, 1H, $J_{5/6}$ = 6.4, $J_{6'/F}$ = 46.7, H-6), 4.96 (dd, 1H, $J_{2/3}$ = 10.7, $J_{3/4}$ = 3.7, H-3), 5.14 (dd, 1H, H-2), 5.35 (dd, 1H, $J_{4/5}$= 1.5, H-4). – ^{13}C-NMR (62 MHz / $CDCl_3$ / TMS): δ = 14.0 (CH_3), 20.5, 20.5, 20.6 (OCO*C*H_3), 22.6–32.7 (CH_2), 67.4 (d, $J_{C-4/F}$ = 5.8, C-4), 69.0 (C-2), 70.3 (CH_2-α), 71.5 (d, $J_{C-5/F}$ = 23.6, C-5), 80.8 (d, $J_{C-6/F}$ = 169.9, C-6), 101.3 (C-1), 169.3, 170.1, 170.2 (O*C*OCH$_3$). – ^{19}F-NMR (235 MHz / $CDCl_3$ / $CFCl_3$): δ_F = –230.5.

c) Dodecyl 6-deoxy-6-fluoro-β-D-galactopyranoside (**17**)

143 mg (0.3 mmol) of **16** were deacetylated as described for **3a–f**. Compound **17** (t.l.c. dichloromethane/methanol 6 : 1 v/v; R_f = 0.52, yield: 90 mg (85.3 %)) was recrystallized from hexane; m.p. 75.5 °C.

$C_{18}H_{35}O_5F$ (350.47) calcd. C 61.69, H 10.07 found C 61.38, H 9.99

^{1}H-NMR (250 MHz / acetone-d_6 / TMS): δ = 0.86 (t, 3H, CH_3), 1.20–1.36 (m, 18H, CH_2), 1.53 (m, 2H, CH_2-β), 3.49 (m, 3H, H-2, H-3,1 CH_2-α), 3.79 (m, 3H, H-4, H-5, 1 CH_2-α), 4.21 (d, 1H, $J_{1/2}$ = 7.6, H-1), 4.52 (ddd, 1H, $J_{5/6}$ = 6.7,

$J_{6/6'}$ = 9.8, $J_{6/F}$ = 48.5, H-6), 4.60 (ddd, 1H, $J_{5/6}$ = 4.6, $J_{6'/F}$ = 46.4, H-6). – ^{13}C-NMR (62 MHz / DMSO-d_6 / TMS): δ = 14.1 (CH_3), 22.3–31.5 (CH_2), 68.4 (d, $J_{C-4/F}$ = 7.1, C-4), 68.9 (CH_2-α), 70.5 (C-2), 73.2 (d, $J_{C-5/F}$ = 20.1, C-5), 73.2 (C-3), 83.6 (d, $J_{C-6/F}$ = 165.5, C-6), 103.5 (C-1). – ^{19}F-NMR (235 MHz / DMSO-d_6 / $CFCl_3$): δ_F = –227.8.

References

[1] a) Part 13.: R. Miethchen, H. Klein, C. Pedersen, Liebigs Ann. Chem. **1994**, 965; b) Amphiphilic and Mesogenic Carbohydrates VII; Part VI.: R. Miethchen, H. Prade, Carbohydr. Lett. **1** (1994) 19

[2] a) N. Sharon, Complex Carbohydrates, 1st. Ed., Addison-Wesley Publ. Comp., Massachusetts 1975; b) R. R. Schmidt, Angew. Chem. **98** (1986) 213; Angew. Chem. Int. Ed. Engl. **25** (1986) 212; c) H. Ringsdorf, B. Schlarb, J. Venzmer, Angew. Chem. **100** (1988) 117; Angew. Chem. Int. Ed. Engl. **27** (1988) 113; d) H. Ogawa, A. Hasegawa, T. Suami (Editors), Carbohydrates, Synthetic Methods and Application in Medical Chemistry, Kodansha-VCH, Tokyo-Weinheim, New York, Cambridge, Basel, **1992**

[3] a) Th. Böcker, J. Thiem, Tenside, Surfactants, Detergents **26** (1989) 318; b) P. Y. Goneth, P. Gogalis, R. Bikanga, P. Gode, D. Postel, G. Ronco, P. Villa, J. Carbohydr. Chem. **13** (1994) 249

[4] a) R. Miethchen, D. Peters, Wiss. Z. Univ. Rostock, Math.-Naturwiss. Reihe **36** (1987) 55; b) R. Miethchen, D. Peters, Z. Chem. **28** (1988) 298; c) R. Miethchen, J. Holz, D. Peters, J. Fluorine Chem. **50** (1990) 217

[5] a) J. W. Goodby, Mol. Cryst. Liq. Cryst. **110** (1984) 205; b) G. A. Jeffrey, Acc. Chem. Res. **19** (1986) 168; c) Y. J. Chung, G. A. Jeffrey, Biochem. Bioorg. Acta. **935** (1989) 300; d) G. A. Jeffrey, L. M. Wingert, Liq. Cryst. **12** (1992) 179

[6] V. Vill, T. Böcker, J. Thiem, F. Fischer, Liq. Cryst. **6** (1989) 349

[7] R. Miethchen, H. Prade, J. Holz, K. Praefcke, D. Blunk, Chem. Ber. **126** (1993) 1707

[8] a) R. Miethchen, J. Holz, H. Prade, A. Lipták, Tetrahedron **48** (1992) 3061; b) W.V. Dahlhoff, K. Riehl, P. Zugenmaier, Liebigs Ann. Chem. **1993**, 1063

[9] a) R. Miethchen, M. Schwarze, J. Holz, Liq. Cryst. **15** (1993) 185; b) The former published thermal data of the dodecyl derivative **8** (ref. [9a]) have to be corrected: m.p. 122–123 °C, c.p. 168.0 °C (S_A)

[10] H. Prade, thesis, University of Rostock, 1994

[11] R. Miethchen, T. Gabriel, D. Peters, J. Holz, M. Michalik, Carbohydr. Res. **214** (1991) 331

[12] D. Cabaret, R. Kazandjan, M. Wakselman, Carbohydr. Res. **149** (1986) 464

[13] R. Miethchen, T. Gabriel, G. Kolp, Synthesis **1991**, 885

[14] a) R. Miethchen, T. Gabriel, Chem. Ber. **126** (1993) 2309; b) R. Miethchen, T. Gabriel, J. Fluorine Chem. **67** (1994) 11

[15] G. Zemplén, A. Gerecz, I. Hadacsy, Ber. Dtsch. Chem. Ges. **69** (1936) 1827

[16] B. Bernet, A. Vasella, Helv. Chim. Acta **62** (1979) 1990

[17] V. I. Betaneli, M. V. Ovchinnikov, L. V. Backinowski, N. K. Kochetkov, Carbohydr. Res. **84** (1980) 211

[18] R. Miethchen, G. Kolp, J. Fluorine Chem. **60** (1993) 49

[19] E. Barrell, B. Grant, M. Oxsen, E. T. Samalski, P. C. Moews, J. R. Knox, R. R. Gaskill, J. L. Haberfeld, Org. Coat. Plast. Chem. **40** (1979) 67

[20] Different references in: a) P. J. Card, J. Carbohydr. Chem. **4** (1985) 451; b) T. Tsuchiya, Adv. Carbohydr. Chem. Biochem. **48** (1990) 91

[21] N. F. Taylor, P. W. Kent, J. Chem. Soc. **1958**, 872

[22] a) H. Kunz, W. Sager, Helv. Chim. Acta **68** (1985) 283; b) H. Kunz, H. Waldmann, J. Chem. Soc., Chem. Commun. **1985**, 638

[23] K. Bock, C. Pedersen, Adv. Carbohydr. Chem. Biochem. **41** (183) 27

[24] R. Csuk, B. I. Glänzer, Adv. Carbohydr. Chem. Biochem. **46** (1988) 73

[25] H. A. van Doren, L. M. Wingert, Mol. Cryst. liq. Cryst. **198** (1991) 381

[26] V. Vill, T. K. Lindhorst, J. Thiem, J. Carbohydr. Chem. **10** (1991) 771

[27] Thermal data of dodecyl α-D-galactopyranoside (**12**): m.p. 70.5–72.5 °C, c.p. 141 °C; R. Miethchen, C. Zur, unpublished results

Address for correspondence
Prof. Dr. Ralf Miethchen
Universität Rostock, Fachbereich Chemie/Organische Chemie
D-18051 Rostock, Germany