*Carbohydrate Research*, 142 (1985) 165–171
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

## Note

# Preparation and n.m.r.-spectral characteristics of benzyl-$\alpha,\alpha$-$d_2$ ethers of monosaccharides

ALEKSANDER ZAMOJSKI*, BARBARA GRZESZCZYK, ANNA BANASZEK, JAKUB BABIŃSKI, XAVIER BORDAS, KRZYSZTOF DZIEWISZEK, AND SŁAWOMIR JAROSZ

*Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warsaw (Poland)*

(Received September 18th, 1984; accepted for publication in revised form, March 11th, 1985)

When used to protect hydroxyl groups of carbohydrates, benzyl groups give derivatives having complex n.m.r. spectra. In their $^1$H-n.m.r. spectra, proton signals of the methylene groups occur as AB quartets in the region $\delta$ 4.5–5.0, where they often overlap with signals of sugar-ring protons. Although high-field $^1$H-n.m.r. spectra often facilitate a full assignment of the signals, there are cases when, even at 500 MHz, the spectra cannot be rationalized, because of overlap of signals. In their $^{13}$C-n.m.r. spectra, the signals of the methylene portion of the *O*-benzyl group normally occur at 70–76 p.p.m., where they coincide with those of pyranose-ring carbon atoms.

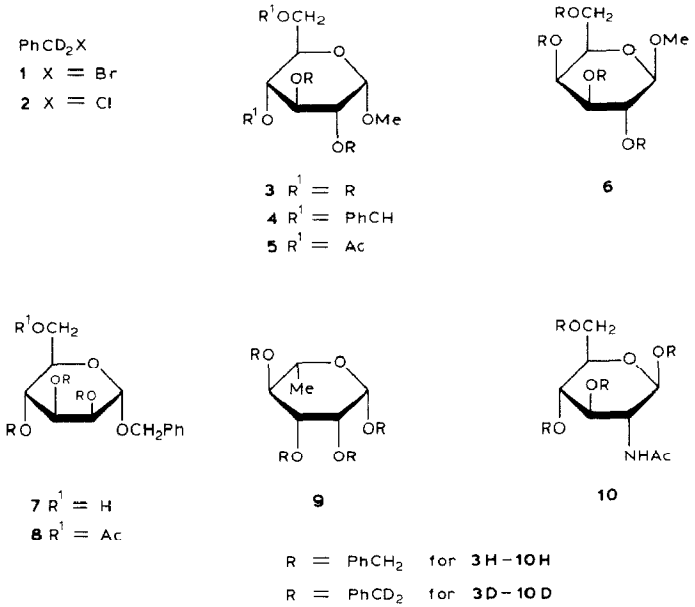
These spectral disadvantages can be avoided by employing benzyl-$\alpha,\alpha$-$d_2$ ($PhCD_2$) instead of normal ($PhCH_2$) benzyl groups. In the $^1$H-n.m.r. spectra, AB lines of the methylene group are absent, and, in the $^{13}$C-n.m.r. spectra, the signals of methylene groups are split, due to coupling, and are weakened to such an extent that they practically "disappear" from the spectrum[1]. Paulsen and co-workers[2,3] drew attention to the advantages of benzyl-$\alpha,\alpha$-$d_2$ groups in carbohydrate chemistry, and proposed the use of benzyl-$\alpha,\alpha$-$d_2$ bromide (**1**) as a reagent for the formation of benzyl ethers of sugars.

We now present a simple and inexpensive method for preparing benzyl-$\alpha,\alpha$-$d_2$ bromide (**1**) and chloride (**2**). Then, the physical properties of a number of monosaccharides respectively protected with normal and $\alpha,\alpha$-dideuterated benzyl groups are compared. For that purpose, derivatives of D-glucose (**3**–**5**), D-galactose (**6**), D-mannose (**7** and **8**), L-rhamnose (**9**), and 2-amino-2-deoxy-D-glucose (**10**) were selected.

Benzyl-$\alpha,\alpha$-$d_2$ bromide[4] (**1**) and chloride[5] (**2**) had earlier been obtained by reduction of methyl or ethyl benzoate with lithium aluminum deuteride, yielding benzyl-$\alpha,\alpha$-$d_2$ alcohol, whose hydroxyl group was then replaced by using bromide or chloride anions. Paulsen and co-workers[2] suggested a less expensive approach to

*To whom correspondence should be addressed.

0008-6215/85/$ 03.30 




**1** consisting in reduction of $\alpha,\alpha,\alpha$-trichlorotoluene with zinc–acetic acid-$d_1$ (AcOD) to toluene-$\alpha,\alpha,\alpha$-$d_3$, and bromination of the latter.

In our method[6], sodium phenylacetate is refluxed with 15–20% sodium deuteroxide in deuterium oxide until the desired degree of H→D exchange has

TABLE I

YIELDS AND PHYSICAL PROPERTIES OF THE MONOSACCHARIDE BENZYL ETHERS **3H–10H** AND **3D–10D**

| *Compound* | *Yield (%)* | *M.p. (degrees)* | *$[\alpha]_D$ (temp., c, solvent)* | *Lit. $[\alpha]_D$ (temp., c, solvent) (Lit.m.p.)* | *References* |
|---|---|---|---|---|---|
| **3H** | 95.7 | [a] | +13.1 (17, 3.4, $CHCl_3$) | +18.7 (25, 1.5, $CHCl_3$) | 9 |
| **3D** | 75.2 | [a] | +15.2 (17, 3.4, $CHCl_3$) | | |
| **4H** | 87.0 | 95.5–96 | −30.9 (20, 2.0, $CHCl_3$) | −30.0 (23, 0.25, $CHCl_3$) | 10 |
| **4D** | 95.0 | 95.5–96 | −31.4 (20, 2.0, $CHCl_3$) | | |
| **5H** | 96.0 | [a] | +18.1 (20, 2.0,$CHCl_3$) | +13.0($CHCl_3$) | 11 |
| **5D** | 94.0 | [a] | −3.7 (20, 2.0,$CHCl_3$) | | |
| **6H** | 65.0 | 79.5–81 | +18.4 (20, 1.3, $C_6H_6$) | +18.0 (20, 3.6, 1,4-dioxane) | 12 |
| **6D** | 74.0 | 84–85 | +22.1 (20, 1.4, $C_6H_6$) | (80–81) | |
| **7H** | 42.4 | [a] | +46.4 (17, 1.8, $CHCl_3$) | +55.0 (20, 1.5, $CHCl_3$) | 13 |
| **7D** | 67.5 | [a] | +53.4 (17, 1.9, $CHCl_3$) | | |
| **8H**[b] | 28.2 | [a] | +42.4 (21, 2.0, $CHCl_3$) | — | — |
| **8D**[b] | 24.4 | [a] | +46.7 (21, 2.0, $CHCl_3$) | | |
| **9H**[c] | 71.0 | 73.5–74 | +92.1 (20, 1.6, $CH_2Cl_2$) | +77 (?, 1.5, $CH_2Cl_2$) | 14 |
| **9D** | 70.0 | 73–74 | +91.9 (20, 1.5, $CH_2Cl_2$) | (74.1) | |
| **10H** | 56.0 | 164–165 | −12.6 (21, 1.1, $CHCl_3$) | −13.4 (20, 1.0, $CHCl_3$) | 15 |
| **10D** | 60.5 | 167–168 | −10.8 (21, 1.1, $CHCl_3$) | (166–167) | |

[a]Syrup. [b]Obtained as a side-product during the preparation of **7H** and **7D**. [c]From the same preparation ~2.5% of the $\alpha$ anomer was obtained $[\alpha]_D^{20}$ −20.4° (*c* 2.6, $CH_2Cl_2$); lit.[14] $[\alpha]_D$ −14.1° (*c* 2.6, $CH_2Cl_2$).

been achieved. Two consecutive exchange operations diminish the protium content in the methylene group to 5–6% *i.e.*, sodium phenylacetate-$\alpha,\alpha$-$d_2$ with 94–95% of deuterium therein is obtained. Further enhancement of the deuterium content is, of course, possible, but is less practicable, because of increased cost.

The next step consists of a Hunsdiecker degradation of phenylacetic-$\alpha,\alpha$-$d_2$ acid in the presence of bromide or chloride anions. From the variety of methods available[7], we chose the approach of Kochi and co-workers; this is inexpensive and gives the halides in good yields. Heating the solution of phenylacetic-$\alpha,\alpha$-$d_2$ acid in benzene with lead tetraacetate and potassium bromide furnished **1** in 74–81% yield. The same reaction, but with lithium chloride, afforded **2** in 75–83% yield.

The preparation of benzyl-$\alpha,\alpha$-$d_2$ ethers of monosaccharides with **1** or **2** does not differ substantially from that wherein normal benzyl halides are employed. The yields of benzylated products are similar (see Table I). Crystalline products exhibit

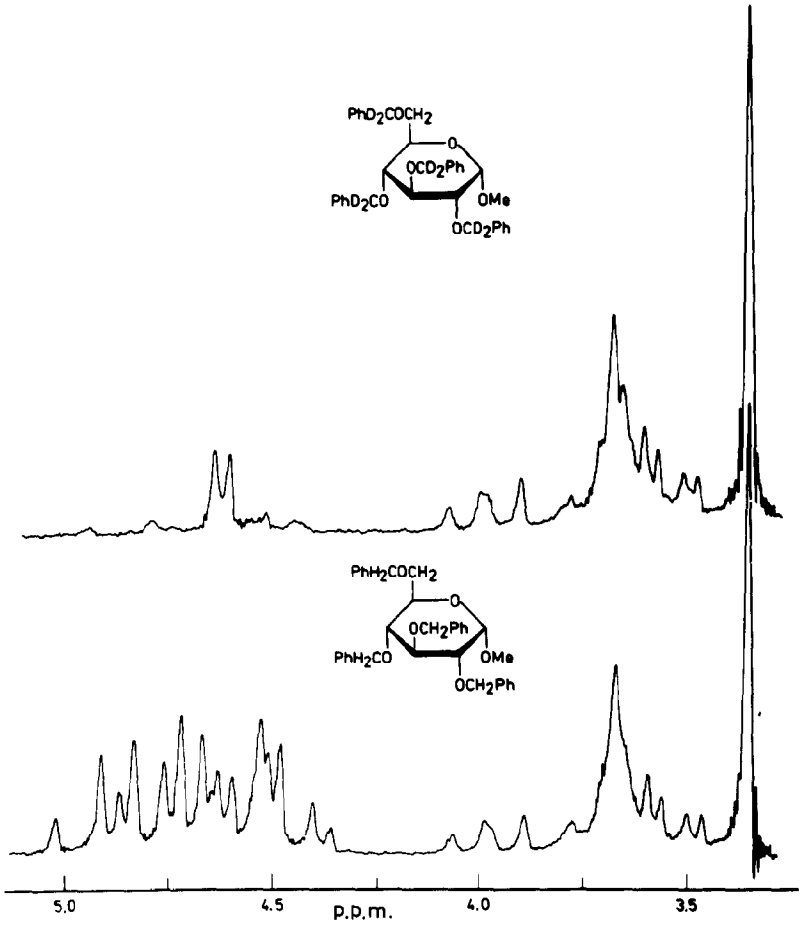



Fig. 1. $^1$H-N.m.r. spectrum of methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (**3H** and **3D**).

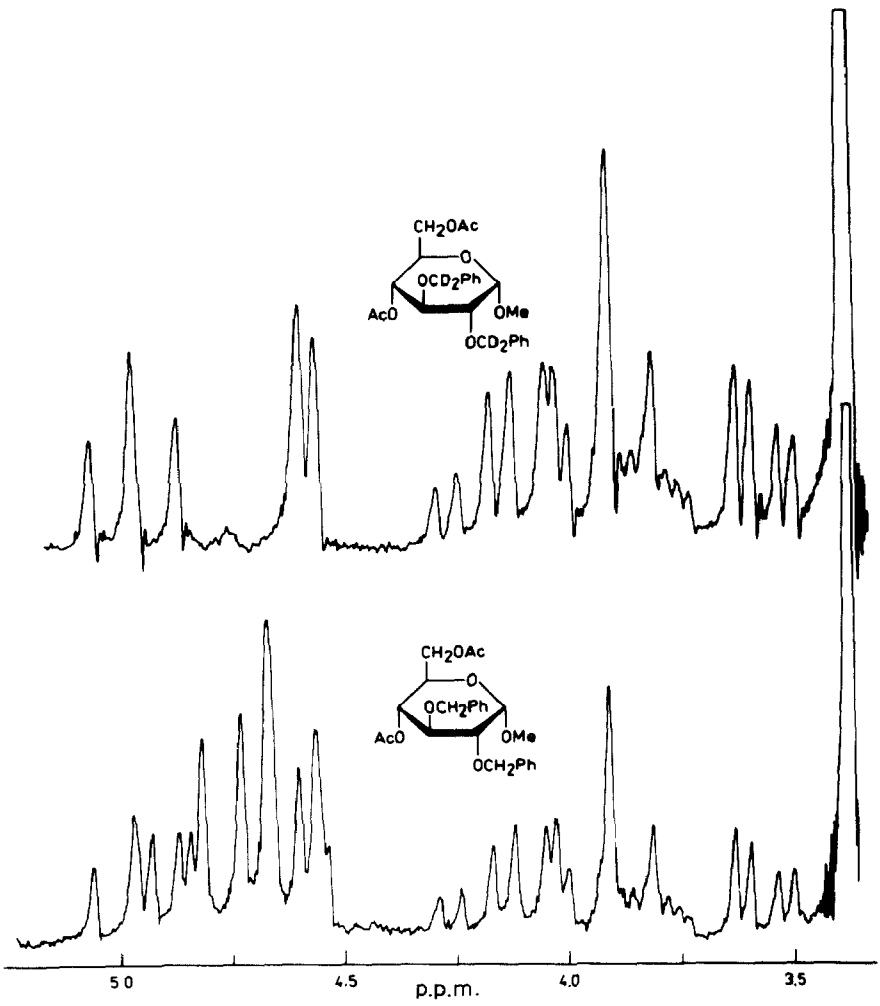



Fig. 2. $^1$H-N.m.r. spectrum of methyl 4,6-di-*O*-acetyl-2,3-di-*O*-benzyl-α-D-glucopyranoside (**5H** and **5D**).

practically the same m.p. values in both series. As the data in Table I show, there are some differences in specific rotation. In the majority of cases, α,α-deuterated benzyl ethers display slightly more positive rotations than their normal relatives. A remarkable difference in specific rotation was noted for the pair **5H,5D**; an accidental mistake was excluded by examination of three independent preparations of **5D**; each sample exhibited the same low-negative $[\alpha]_D$ value.

The i.r. spectra in chloroform solution are similar for the compounds of both series. In the spectra of α,α-dideuterated benzyl ethers, low intensity bands occur at 2195, 2175, 2135, 2090, and 2070 $cm^{-1}$, specific for C–D bonds.

Two illustrations of $^1$H-n.m.r. spectra (see Figs. 1 and 2) demonstrate clearly the advantages of benzyl-α,α-$d_2$ ethers in proton-resonance spectra. The ring-pro-

TABLE II

$^{13}$-C CHEMICAL SHIFT VALUES FOR MONOSACCHARIDE BENZYL ETHERS **3H–10H** AND **3D–10D**

| *Compound* | *Carbon atom* | | | | | | *$PhCH_2O$* | *Other signals* |
|---|---|---|---|---|---|---|---|---|
| | *1* | *2* | *3* | *4* | *5* | *6* | | |
| **3H** | 98.22 | 79.92 | 82.16 | 77.72 | 70.10 | 68.55 | 75.72, 74.98, 73.47, 73.37 | $OCH_3$: 55.14 |
| **3D** | 98.23 | 79.82 | 82.09 | 77.65 | 70.12 | 68.47 | | $OCH_3$: 55.14 |
| **4H** | 99.25 | 79.24 | 78.62 | 82.17 | 62.34 | 69.06 | 75.29, 73.76 | Ph*C*H: 101.26, $OCH_3$: 55.31 |
| **4D** | 99.27 | 79.13 | 78.52 | 82.17 | 62.33 | 69.06 | | Ph*C*H: 101.26, $OCH_3$: 55.31 |
| **5H** | 98.30 | 79.63 | 79.15 | 67.58 | 69.78 | 62.36 | 75.41, 73.58 | $CH_3CO$: 20.72, $OCH_3$: 55.42 |
| **5D** | 98.33 | 79.54 | 79.06 | 67.57 | 69.78 | 62.35 | | $CH_3CO$: 20.71, $OCH_3$: 55.41 |
| **6H** | 105.04 | 79.65 | 82.21 | 73.57 | 73.42 | 68.89 | 75.09, 74.49, 73.57, 73.03 | $OCH_3$: 56.95 |
| **6D** | 105.05 | 79.59 | 82.11 | 73.46 | 73.46 | 68.92 | | $OCH_3$: 56.95 |
| **7H** | 97.59 | 74.94 | 80.20 | 74.94 | 72.49 | 62.35 | 75.24, 72.91, 72.30 | 1-Ph$CH_2O$: 69.13 |
| **7D** | 97.60 | 74.85 | 80.14 | 74.85 | 72.50 | 62.34 | | 1-Ph$CH_2O$: 69.13 |
| **8H** | 97.25 | 74.61 | 80.21 | 74.61 | 70.38 | 63.60 | 75.23, 72.61, 72.19 | 1-Ph$CH_2O$: 69.22, $CH_3CO$: 20.88 |
| **8D** | 97.26 | 74.51 | 80.14 | 74.51 | 70.36 | 63.61 | | 1-Ph$CH_2O$: 69.19, $CH_3CO$: 20.90 |
| **9H** | 100.28 | 73.96 | 82.35 | 80.21 | 72.01 | 18.01 | 75.39, 74.14, 71.42, 70.78 | |
| **9H** | 100.20 | 73.88 | 82.24 | 80.12 | 72.01 | 18.02 | | |
| **10H** | 99.28 | 56.43 | 80.43 | 78.52 | 74.89 | 69.13 | 74.43 (2×), 73.48, 70.70 | $CH_3CO$: 23.49 |
| **10D** | 99.27 | 56.37 | 80.45 | 78.40 | 74.85 | 68.97 | | $CH_3CO$: 23.47 |

ton signals of benzylated sugars, such as that of anomeric or of $RCO_2CH$ protons, which usually overlap with methylene-group quartets, now appear as clear, well analyzable multiplets. The baseline between $\delta$ 4.5 and 5.0 showed some irregularity, due to the fact that the **1** and **2** used for the preparation of the benzyl-$\alpha,\alpha$-$d_2$ ethers contained ~5% of protons.

The $^{13}$C-n.m.r.-spectral data for compounds **3H–10H** and **3D–10D** are summarized in Table II. The resonance signals were assigned to particular carbon atoms of the pyranose ring according to literature data[16]. The absorptions of methylene-group carbon atoms ($PhCH_2O$) were obtained by simple subtraction of the two respective spectra. As expected, these signals occur in the region 70–75 p.p.m. In the spectra of **3D–9D**, an isotope $\gamma$-effect of $\sim -0.1$ p.p.m. may be observed. For the 2-amino-2-deoxy-D-glucose derivative **10D**, this effect is seen for carbon atoms that are non-vicinal to C-2, *i.e.*, for C-4 and C-6. Here, this effect is larger, and amounts to $\sim -0.15$ p.p.m. Of importance is the fact that this effect facilitates the assignment of signals of carbon atoms bearing benzyl groups (*e.g.*, in pairs **4H,4D** and **5H,5D**).

## EXPERIMENTAL

$^1$H-N.m.r. spectra were recorded with Jeol JNM-4H-100 (100 MHz) and Varian XL-200 (200 MHz) spectrometers, and $^{13}$C-n.m.r. spectra with a Varian CFT-20 spectrometer. Deuteriochloroform was used as the solvent, and tetramethylsilane as the internal standard. Optical rotations were measured with a Perkin–Elmer 141 automatic polarimeter. Compounds **3H,D–10H,D** were prepared according to the literature (see Table I for references).

*Phenylacetic-$\alpha,\alpha$-$d_2$ acid.* — Dry sodium phenylacetate (49 g, prepared from commercial phenylacetic acid) was dissolved in deuterium oxide (30 mL, deuterium content, 99.92%) containing sodium deuteroxide (5.2 g), and the mixture was boiled under reflux for 2 h. The solution was cooled and evaporated to dryness, a fresh portion (30 mL) of $D_2O$ added, and the refluxing continued for an additional 2 h. The $^1$H-n.m.r. spectrum of the solution showed 5 ±1% of proton content in the methylene group. The solution was acidified with hydrochloric acid and extracted with benzene. The benzene solution of phenylacetic-$\alpha,\alpha$-$d_2$ acid was dried, and used for the next step.

*Benzyl-$\alpha,\alpha$-$d_2$ bromide* (**1**). — The following preparation is a modified version of the method of Kochi *et al.*[8]. A solution of phenylacetic-$\alpha,\alpha$-$d_2$ acid (27.2 g, 0.2 mol) in benzene (125 mL) was mixed with lead tetraacetate (128 g, 0.29 mol) and potassium bromide (38.1 g, 0.32 mol), benzene (300 mL) was added, and the mixture was stirred under nitrogen or argon. After 1 h, the orange solution was heated, and, at 60–65° evolution of carbon dioxide started. The mixture was boiled under reflux for ~1 h, cooled, treated with 15% hydrochloric acid (~200 mL), and the layers separated. The benzene solution was successively washed with water and 10% aq. sodium hydrogencarbonate, dried (magnesium sulfate), and evaporated,

and the residue distilled at 64–66°/933 Pa, to give 25.3 g (74.3%) of **1**. According to the $^1$H-n.m.r. spectrum and gas–liquid chromatography, the product contained ~5% of benzyl-$\alpha,\alpha$-$d_2$ acetate. We found that this contamination does not affect the course of etherification of saccharides. The residual, $^1$H-n.m.r. signal of the methylene group, at $\delta$ 4.44, indicated a hydrogen content of 5 ±1%.

*Benzyl-$\alpha,\alpha$-$d_2$ chloride* (**2**). — The preparation of **2** was analogous to the synthesis of **1**. From 27.2 g (0.2 mol) of phenylacetic-$\alpha,\alpha$-$d_2$ acid, 142 g (0.32 mol) of lead tetraacetate, and 13.6 g (0.32 mol) of lithium chloride was obtained 21 g (83%) of **2** on distillation at 47–48°/933 Pa. In its $^1$H-n.m.r. spectrum the product displayed the residual methylene-group signal at $\delta$ 4.47, corresponding to a hydrogen content of 5 ±1%.

ACKNOWLEDGMENTS

This work was supported by Grant No. MR-I.12.1.7.4. One of us (X.B.) is grateful for a stipend provided in the Polish–Spanish Scientific Exchange Programme. We thank Professor K. Jankowski (Moncton, N.B., Canada) for recording the 200-MHz, $^1$H-n.m.r. spectra.

REFERENCES

1 For references, see P. A. J. Gorin, A. P. Tulloch, and M. Mazurek, *Carbohydr. Res.*, 117 (1983) 279–284.
2 H. Paulsen, W. Röben, and F. R. Heiker, *Tetrahedron Lett.*, (1980) 3679–3680.
3 H. Paulsen and A. Bünsch, *Justus Liebigs Ann. Chem.*, (1981) 2204–2215.
4 R. L. Letsinger and D. F. Pollart, *J. Am. Chem. Soc.*, 78 (1956) 6079–6085.
5 S. Meyerson, P. N. Rylander, Jr., E. L. Eliel, and J. D. McCollum, *J. Am. Chem. Soc.*, 81 (1959) 2606–2610.
6 Polish Pat. Appl. No. P-246882.
7 C. V. Wilson, *Org. React.*, 9 (1957) 332–387; R. C. Cambie, R. C. Hayward, J. L. Jurlina, P. S. Rutledge, and P. D. Woodgate, *J. Chem. Soc., Perkin Trans. 1*, (1981) 2608–2614; D. Crich, D. H. R. Barton, and W. B. Motherwell, *Tetrahedron Lett.*, (1983) 4979–4982.
8 J. K. Kochi, *J. Org. Chem.*, 30 (1965) 3265–3271; J. D. Bacha and J. K. Kochi, *ibid.*, 33 (1968) 83–93; R. A. Sheldon and J. K. Kochi, *Org. React.*, 19 (1972) 279–421.
9 M. E. Tate and C. T. Bishop, *Can. J. Chem.*, 41 (1963) 1801–1806.
10 A. G. M. Barret, R. W. Read, and D. H. R. Barton, *J. Chem. Soc., Perkin Trans. 1*, (1980) 2184–2190.
11 H. B. Borén, P. J. Garegg, L. Kenne, Å. Pilotti, S. Svensson, and C. G. Swahn, *Acta Chem. Scand.*, 27 (1973) 2740–2748.
12 P. W. Austin, F. E. Hardy, J. G. Buchanan, and J. Baddiley, *J. Chem. Soc.*, (1965) 1419–1424.
13 J. Alais and A. Veyrières, *Carbohydr. Res.*, 92 (1981) 310–313.
14 H. Paulsen, W. Kutschker, and O. Lockhoff, *Chem. Ber.*, 114 (1981) 3233–3241.
15 J. R. Plimmer, N. Pravdić, and H. G. Fletcher, Jr., *J. Org. Chem.*, 32 (1967) 1982–1984.
16 E. Breitmaier and W. Voelter, *$^{13}$C-NMR Spectroscopy*, Verlag Chemie, Weinheim, 1974, pp. 223–242.