Carbohydrate Research, 49 (1976) 482–488

Note

The synthesis of derivatives of *O*-(2-acetamido-2-deoxy-D-glucopyranosyl)-L-serine*†

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(Received December 16th, 1975; accepted for publication, December 22nd, 1975)

Mono- and oligo-saccharide residues may be of value for enhancing the immunonogenicity of weakly immunogenic, synthetic polypeptides[1]. In addition, these synthetic glycopeptides may serve as standard compounds in the study of the base-catalyzed β-elimination of carbohydrate residues of the mucin-type glycoproteins and of proteoglycans[2].

In the syntheses[3,4] of *O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-*N*-(benzyloxycarbonyl)-L-serine methyl ester (**3**), only a syrupy product was obtained, whereas the benzyl ester analog (**10**) was obtained in crystalline form[4,5]. For this reason, the Koenigs–Knorr condensation[6] of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride[7] (**5**) with *N*-(benzyloxycarbonyl)-L-serine methyl ester[8] (**6**) and with *N*-(benzyloxycarbonyl)-L-serine benzyl ester[9] (**7**), as modified by Helferich and Wedemeyer[10] (*i.e.*, with mercuric cyanide as an acid acceptor), was investigated.

In the elongation of the peptide chain towards the C-terminal, alkaline conditions[11] are required to hydrolyze the methyl ester group of **3**, whereas the benzyl ester group of **10** requires only hydrogenolysis[11]. This group, however, is labile under acidic conditions, and the *p*-nitrobenzyl ester **9** was prepared, since the *p*-nitrobenzyl group shows a marked resistance to acid cleavage[12].

Treatment of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride (**5**) with *N*-(benzyloxycarbonyl)-L-serine methyl ester (**6**) in the presence of mercuric cyanide as acid acceptor gave **3** in crystalline form. The n.m.r. spectrum showed the expected β-D-anomeric proton at δ 5.75 with a coupling constant $J_{1,2}$

*Dedicated to the memory of Professor Edward J. Bourne.

†Amino sugars C. This is publication No. 697 of the Robert W. Lovett Memorial Group for the Study of Diseases Causing Deformities, Harvard Medical School at the Massachusetts General Hospital, Boston, Massachusetts. This work was supported by research grants from the National Institute of Arthritis, Metabolism and Digestive Diseases (AM-03564 and -05067) and from the National Cancer Institute (CA-08418), National Institutes of Health, U.S. Public Health Service.

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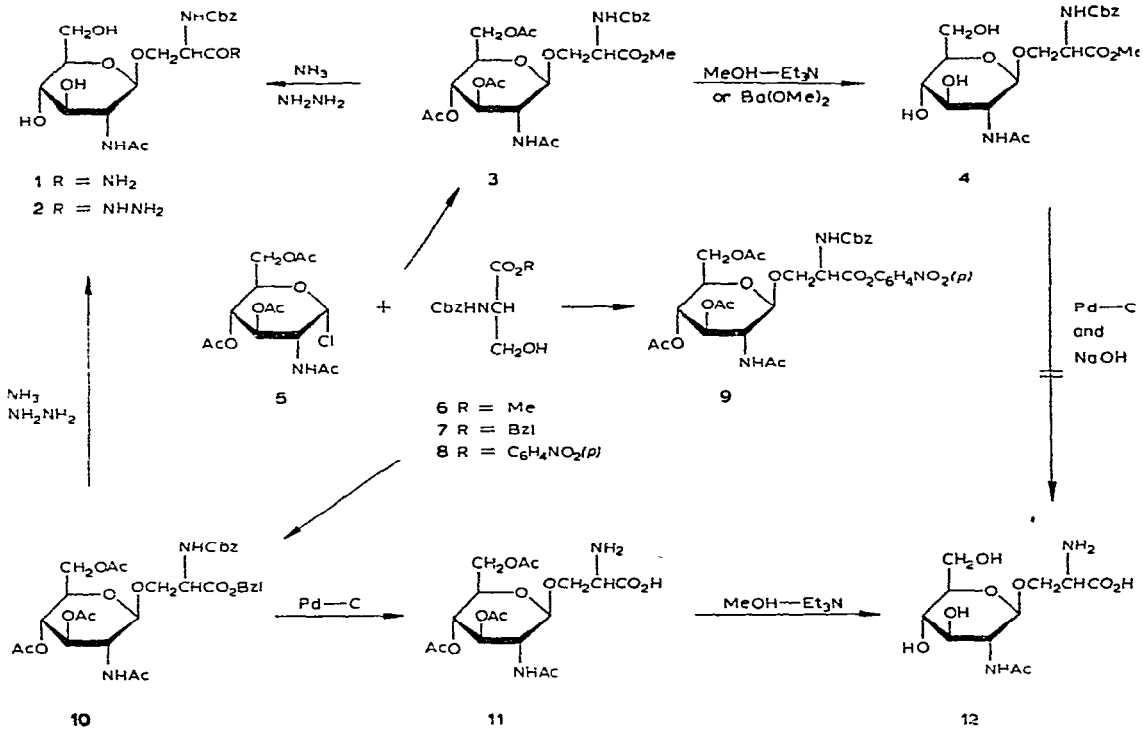

9.5 Hz. Similarly, treatment of *N*-(benzyloxycarbonyl)-L-serine benzyl ester (**7**) and *N*-(benzyloxycarbonyl)-L-serine *p*-nitrobenzyl ester (**8**) with **5** gave crystalline *O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-*N*-(benzyloxycarbonyl)-L-serine benzyl ester (**10**) and *O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-*N*-(benzyloxycarbonyl)-L-serine *p*-nitrobenzyl ester (**9**), respectively.

Treatment of the methyl ester **3** or the benzyl ester **10** with ammonia gave the same *O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-*N*-(benzyloxycarbonyl)-L-serine amide (**1**), while treatment of **5** or **6** with hydrazine resulted in the same *O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)- *N*-(benzyloxycarbonyl)-L-serine hydrazide (**2**). Treatment of **3** with barium methoxide in methanolic solution gave *O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-*N*-(benzyloxycarbonyl)-L-serine methyl ester (**4**).

Hydrogenolysis of **10** in the presence of 10% palladium-on-charcoal gave *O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-L-serine (**11**), which was *O*-deacetylated with triethylamine to give *O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-L-serine[4] (**12**). Attempts to prepare **12** by hydrogenolysis of **4** in the presence of 10% palladium-on-charcoal followed by alkaline hydrolysis were unsuccessful.

In the elucidation of the chemical structure of mucin-type glycoproteins or proteoglycans, the liberation of oligosaccharide chains may be incomplete because

these chains are linked to a serine or threonine residue located at the C-terminal residue or a residue that became C-terminal, under the alkaline conditions, before the carbohydrate chain was released. Blocking of the carboxyl group may restore the conditions required for β-elimination. When **1**, **2**, **3**, and **12** were treated for β-elimination under conditions similar to those described by Mayo and Carlson[13], it was found (see Table I) that, as expected, no carbohydrate residue was released from **12** having a free carboxyl group and that the methyl ester group of **3** was hydrolyzed before any appreciable liberation of the carbohydrate residue took place. Both the amide (**1**) and the hydrazide groups (**2**) provide excellent protection, and the recovery of DL-alanine, derived from L-serine, and of 2-acetamido-2-deoxy-D-glucitol, derived from 2-acetamido-2-deoxy-D-glucose, was in the range of the previously reported yields[13].

TABLE I

TREATMENT OF COMPOUNDS **1**, **2**, **3**, AND **12** UNDER THE CONDITIONS OF THE β-ELIMINATION[a]

Compounds treated	*Compounds obtained after hydrolysis*[b] (%)			
	L-*Serine*	DL-*Alanine*	*2-Acetamido-2-deoxy-D-glucose*	*2-Acetamido-2-deoxy-D-glucitol*
1	5	45	6	68
2	6	40	6	69
3	70	21	67	9
12	100	0	81	3

[a]2M Sodium borohydride and 50mM sodium hydroxide for 20 h at 40°. [b]With 2M hydrochloric acid for 2 h at 100°.

EXPERIMENTAL

General. — Evaporations were performed *in vacuo*. Melting points were determined with a Mettler FP-2 apparatus and correspond to "corrected melting points". Rotations were determined for solutions in 1-dm semimicro tubes with a Perkin–Elmer Model 141 polarimeter. The *N*,*N*-dimethylformamide used was spectro-reagent grade. I.r. spectra were recorded, for potassium bromide discs, with a Perkin–Elmer spectrophotometer Model 237. The homogeneity of compounds was verified by ascending t.l.c. on precoated plates of Silica Gel (Merck) with solvents (v/v): *A* (19:1 chloroform–methanol), *B* (19:1 chloroform–ethanol), *C* (7:3 chloroform–methanol), and *D* (4:7 chloroform–methanol); the spots were detected by spraying with 20% sulfuric acid and heating at 200° for a few min. With free amino glycopeptides, the spots were detected by spraying with a ninhydrin solution in acetone and heating for a few sec. The n.m.r. spectra were recorded with a Varian T-60 instrument for solutions in chloroform-*d*, with tetramethylsilane as internal standard. The microanalyses were performed by Dr. W. Manser, Zürich, Switzerland.

O-(*2-Acetamido-3,4,6-tri*-O-*acetyl-2-deoxy-β*-D-*glucopyranosyl*)-N-(*benzyloxycarbonyl*)-L-*serine methyl ester* (**3**). — To a solution of *N*-(benzyloxycarbonyl)-L-serine methyl ester[8] (**6**, 7.6 g) in benzene (100 ml), previously dried by distillation of 25 ml of benzene, were added mercuric cyanide (8.0 g) and benzene (50 ml), and 25 ml of benzene were distilled off. 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride[7] (**5**, 11.2 g) was added, and the stirred mixture was boiled for 8 h under reflux and then kept for 24 h at room temperature. The dark-brown solution was evaporated and the residue extracted with chloroform (250 ml). The chloroform layer was washed many times with 30% aqueous potassium iodide and water, dried (sodium sulfate), and evaporated to give a syrup that crystallized from methanol–ether to yield **3** as small needles (6.0 g, 34%), m.p. 170–170.5° $[\alpha]_D^{22}$ −9.0° (*c* 1.1, chloroform); i.r. data: ν_{max}^{KBr} 3350–3300 (NH), 1760 (OAc), 1680, (Cbz CO), and 1660–1525 cm^{-1} (peptide Amide I); t.l.c. (Solvent *A*): R_F 0.64; the n.m.r. data were in agreement with those expected for **3**: δ 5.75 (d, 1 H, $J_{1,2}$ 9.5 Hz, H-1), 1.83, 2.00, 2.05 (3 s, 12 H, 3 $COCH_3$, 1 $NHCOCH_3$), 3.75 (s, 3 H, OCH_3), 5.15 (s, 2 H, $C_6H_5CH_2$), and 7.25 (s, 5 H, C_6H_5).

Anal. Calc. for $C_{26}H_{34}N_2O_{13}$: C, 53.60; H, 5.88; N, 4.81; O, 35.71. Found: C, 53.58; H, 5.82; N, 4.71; O, 35.83.

O-(*2-Acetamido-3,4,6-tri*-O-*acetyl-2-deoxy-β*-D-*glucopyranosyl*)-N-(*benzyloxycarbonyl*)-L-*serine benzyl ester* (**10**). — A solution of *N*-(benzyloxycarbonyl)-L-serine benzyl ester[9] (**7**, 3.0 g) in benzene (100 ml) was treated with mercuric cyanide (2.5 g) in benzene (25 ml), and 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride[7] (**5**, 3.3 g), as described for the preparation of **3**. Crystallization from 2-propanol gave 2.8 g (70%) of **10**, m.p. 159–159.5°, $[\alpha]_D^{20}$ −8.9° (*c* 0.8, chloroform); i.r. data: ν_{max}^{KBr} 3380–3320 (NH), 1760 (OAc), 1685 (Cbz CO), and 1660–1525 cm^{-1} (peptide Amide I); t.l.c. (Solvent *B*): R_F 0.6; n.m.r. data: δ 1.85, 2.00, 2.20, (3 s, 12 H, 3 $COCH_3$, and 1 $NHCOCH_3$), 5.14, 5.20 (2 s, 4 H, $C_6H_5CH_2OCO$ and $C_6H_5CH_2$), 5.75 (d, 1 H, $J_{1,2}$ 9.5 Hz, H-1), and 7.25 (s, 10 H, 2 C_6H_5); lit.: m.p. 160°, $[\alpha]_D^{24}$ −9° (chloroform)[4]; m.p. 160–161°, $[\alpha]_D^{23}$ −13.9° (acetic acid)[5].

O-(*2-Acetamido-3,4,6-tri*-O-*acetyl-2-deoxy-β*-D-*glucopyranosyl*)-N-(*benzyloxycarbonyl*)-L-*serine* p-*nitrobenzyl ester* (**9**). — A solution of *N*-(benzyloxycarbonyl)-L-serine *p*-nitrobenzyl ester[14] (**4**, 3.7 g) in benzene (150 ml) was treated with mercuric cyanide (2.5 g) in benzene (50 ml), and 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride[7] (**5**, 3.7 g), as described for the preparation of **3**, except that the mixture was boiled overnight. Crystallization from ethanol gave 1.1 g (15%) of **9**, m.p. 156.5–157°, $[\alpha]_D^{20}$ −18.6° (*c* 0.5, chloroform); i.r. data: ν_{max}^{KBr} 3325 (NH), 1740 (OAc), 1690 (Cbz CO), 1710–1525 (peptide Amide I), and 1350 cm^{-1} (NO_2); t.l.c. (Solvent *B*): R_F 0.39; n.m.r. data: δ 1.90, 2.00, 2.05 (3 s, 12 H, 3 $COCH_3$ and 1 $NHCOCH_3$), 5.10, 5.23 [2 s, 4 H, $C_6H_5CH_2OCO$ and $CH_2C_6H_4NO_2(p)$], 5.75 [d, 1 H, $J_{1,2}$ 9.0 Hz), and 7.23 [s, 9 H, C_6H_5OCO and $CH_2C_6H_4NO_2(p)$].

Anal. Calc. for $C_{32}H_{37}N_3O_{15}$: C, 54.62; H, 5.29; N, 5.97; O, 34.10. Found: C, 54.54; H, 5.27; N, 5.89; O, 34.14.

O-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-N-(benzyloxycarbonyl)-L-serine amide (**1**). — (*a*) *From* **3**. Dry ammonia gas was passed for 30 min through a solution of **3** (0.5 g) in methanol (50 ml) kept at 0°. After 30 min at room temperature, the solution was evaporated and the residue was crystallized from methanol–ether to give 0.25 g (66%) of **1**, m.p. 249–250° (dec.). Further recrystallization from ethanol–water raised the m.p. to 253–254° (dec.), $[\alpha]_D^{23}$ −41° (*c* 0.5, 1:1, v/v, methanol–water); i.r. data: ν_{max}^{KBr} 3300–3175 (NH, OH), 1675 (Cbz CO group), and 1650–1500 cm^{-1} (peptide Amide I); t.l.c. (Solvent *C*): R_F 0.4; lit.[4]: m.p. 122°, $[\alpha]_D^{24}$ +7° (methanol).

Anal. Calc. for $C_{19}H_{27}N_3O_9$: C, 51.68; H, 6.17; N, 9.52; O, 32.63; Found: C, 51.73; H, 6.24; N, 9.17; O, 32.45.

(*b*) *From* **10**. Dry ammonia gas was passed for 30 min through a solution of **10** (0.25 g) in methanol (150 ml) kept at 0°. After 1 h at room temperature, the solution was evaporated and the residue was crystallized from methanol–ether to give 75 mg (45%) of **1**, m.p. 245–247° (dec.); the i.r. spectra and t.l.c. mobility were identical with those of the compound obtained from **3**.

O-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-N-(benzyloxycarbonyl)-L-serine hydrazide (**2**). — (*a*) *From* **3**. A solution of **3** (2.0 g) and 95% hydrazine (2 ml) in ethanol (20 ml) was heated for a few min and then overnight at room temperature. The crystals were filtered off, and recrystallized from methanol–water to give **2** as fine needles (1.1 g, 70%), m.p. 254–255° (dec.), $[\alpha]_D^{20}$ −18.5° (*c* 1.1, *N,N*-dimethylformamide); i.r. data: ν_{max}^{KBr} 3350–3275 (NH, OH), 1690 (Cbz CO), and 1650–1550 cm^{-1} (peptide Amide I).

Anal. Calc. for $C_{19}H_{28}N_4O_9$: C, 49.99; H, 6.18; N, 12.27; O, 31.55. Found: C, 49.90; H, 6.19; N, 12.30; O, 31.42.

(*b*) *From* **10**. A solution of **10** (0.5 g) and 95% hydrazine (0.5 ml) in ethanol (5 ml) was treated as in (*a*) to give 0.3 g (86%) of **2**, m.p. 254–255° (dec.); the i.r. data were identical with those of the compound obtained in (*a*).

O-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-N-(benzyloxycarbonyl)-L-serine methyl ester (**4**). — (*a*) Triethylamine (2.5 ml) was added to a solution of **3** (0.5 g) in methanol (22.5 ml). After 24 h at room temperature, the solution was evaporated, and the residue was crystallized from absolute ethanol to give 0.15 g (38%) of **4**, m.p. 195–197° (dec.), $[\alpha]_D^{23}$ −22° (*c* 1.3, ethanol); i.r. data: ν_{max}^{KBr} 3425–3300 (NH, OH), 1680 (Cbz CO), and 1675–1550 cm^{-1} (peptide Amide I); t.l.c. (Solvent *D*): R_F 0.4; lit.[3]: m.p. 133°, $[\alpha]_D^{23}$ +6.4° (ethanol).

Anal. Calc. for $C_{20}H_{28}N_2O_{10}$: C, 52.62; H, 6.18; N, 6.14; O, 35.05. Found: C, 52.60; H, 6.20; N, 6.06; O, 34.80.

(*b*) To a solution of **3** (0.5 g) in methanol (20 ml) was added 0.5M barium methylate (2 ml). After 24 h at room temperature, the solution was de-ionized by stirring with Dowex 50 (H^+) resin. After evaporation, the residue showed on t.l.c. (Solvent *D*) two main spots having R_F 0.4 and 0.01 (the latter spot corresponding to that of 2-acetamido-2-deoxy-D-glucose). Crystallization from absolute ethanol gave 0.15 g (38%) of **4**, m.p. 201–202° (dec.; shrinking at 195–197°); the i.r. spectra and t.l.c. mobility were identical with those of the compound obtained in (*a*).

O-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-L-serine (**11**). — A solution of **10** (0.5 g) in 9:1 ethanol–water (100 ml) was hydrogenated in the presence of 10% palladium-on-charcoal (50 mg) for 2 h at room temperature and at a pressure of 1.2 kg.cm^{-2}. The catalyst was filtered off, and the filtrate evaporated to dryness. Crystallisation of the residue from ethanol gave **11** (0.3 g, 90%), m.p. 162–163° (dec.), $[\alpha]_D^{22}$ −38° (*c* 0.5, methanol); i.r. data: ν_{max}^{KBr} 3400 (broad, NH, OH), 1750 (OAc), and 1625–1540 cm^{-1} (peptide Amide I); t.l.c. (Solvent *D*): R_F 0.16; lit.[5]: m.p. 160–162° (dec.), $[\alpha]_D^{23}$ −47.3° (methanol).

O-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-L-serine (**12**). — Triethylamine (2 ml) was added to a solution of **11** (0.2 g) in methanol (18 ml). After 24 h at room temperature, the solution was de-ionized by stirring with Dowex 50 (H^+) resin, and evaporated. The residue was crystallized from ethanol–hexane to give 70 mg of **12** (49%), m.p. 234–236° (dec.), $[\alpha]_D^{22}$ −36.5° (*c* 0.5, water): lit.: m.p. 236°, $[\alpha]_D^{24}$ −31.0° (water)[3]; m.p. 234°, $[\alpha]_D^{22}$ −30° (water)[4].

β-Elimination reaction. — The glycopeptide (400 μg; **1**, **2**, **3**, or **12**) was treated with 2M sodium borohydride in a 0.5M sodium hydroxide solution (200 μl) for 20 h at 40°. The reaction was stopped by addition of acetic acid (2–3 drops). Methanol (0.5 ml) was added, and the solution was concentrated (hot water-bath) to dryness under a stream of nitrogen. Methanol was added several times to the residue and evaporated in order to remove the borate ions. The residue was hydrolyzed by heating with 2M hydrochloric acid for 2 h at 110°. The solution was evaporated and the residue dried in a high vacuum in the presence of sodium hydroxide pellets. The residue was treated with 3M hydrogen chloride in 1-butanol (0.5 ml) for 1 h at 100°, and then with 1:3 (v/v) trifluoroacetic anhydride–dichloromethane (100 μl) for 2 h at 100°. Blanks (0 min of treatment) not exposed to 2M sodium borohydride–0.5M sodium hydroxide were treated in the same manner. G.l.c. of alanine and serine was performed with a Perkin–Elmer Model 900 gas chromatograph on a 1.5-m column of Tabsorb (Regis Chemical Co., Chicago, Illinois 60610), programmed for a rise of 4° per min from 100 to 225°. G.l.c. of 2-acetamido-2-deoxy-D-glucose and 2-acetamido-2-deoxy-D-glucitol was performed with the same instrument on a 1.5-m mixed-phase column of 2% of OV-17 and 1% of OV-210 (Supelco Inc., Bellefonte, Pennsylvania 16823), programmed for a rise of 6.5° per min from 75 to 225°. L-Proline was added to the hydrolyzate as standard. The results are reported in Table I.

AKNOWLEDGMENT

The authors thank Mr. K. Linsley for performing the g.l.c. analysis.

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Added in proof:

In a publication that came to our attention after the present publication had been accepted, Antonenko *et al.*[1] reported that condensation of 2-methyl-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyrano)-[2′,1′:4,5]-2-oxazoline with the methyl ester of *N*-(benzyloxycarbonyl)-L-serine (**6**) gave **3** (72%), m.p. 198°, $[\alpha]_D^{20}$ +33° (methanol).

Since these properties are not in agreement with those reported in the present publication, we have re-examined the reaction of 2-methyl-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyrano)-[2′,1′:4,5]-2-oxazoline (0.99 g), prepared according to the method of Lemieux and Driguez[2], and **6** (1.5 g) in the presence of *p*-toluenesulfonic acid (30 mg) in boiling toluene (18 ml) for 30 min. In contrast to the observations reported by Antonenko *et al.*[1], no precipitate of **3** was obtained. Consequently, the dark, brown solution was evaporated. The residue was extracted with ethyl acetate, washed with water and 1% aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated to give a syrup that crystallized from ethanol to give **3** (410 mg, 34%), m.p. 169–170°, $[\alpha]_D^{21}$ −15.7° (*c* 1.1, methanol), $[\alpha]_D^{21}$ −6.7° (*c* 1.4, chloroform); in admixture with the sample of **3** previously obtained, the m.p. was not depressed; the i.r. spectra, n.m.r. spectra, and t.l.c. mobility were identical with those reported in the present publication. The previously obtained **3** had $[\alpha]_D^{21}$ −15.6° (*c* 1.6, methanol).

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