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Synthesis of methyl *O*-α-L-rhamnopyranosyl-(1 → 2)-α-D-galactopyranosides specifically deoxygenated at position 3, 4, or 6 of the galactose residue †

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ABSTRACT

The title disaccharides were synthesized by condensation of 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide with suitably protected, deoxygenated derivatives of methyl α-D-galactopyranoside. Deoxygenation was achieved via activation of a protected methyl α-D-gluco- or galacto-pyranoside with *N*,*N*′-thiocarbonyldiimidazole followed by treatment with tributyltin hydride and azobisisobutyronitrile. At position 3, the deoxygenation was more successful when performed with the tri-*O*-benzoylated precursor, rather than the tri-*O*-benzylated one. The corresponding nucleophile was obtained by benzylidenation of the methyl 3-deoxy-α-D-xylo-hexopyranoside. The preparation of the glycosyl acceptor deoxygenated at position 4 could be pursued starting from derivatives having either the D-*galacto* or the D-*gluco* configuration. The pathway involving the former was found superior.

INTRODUCTION

Among the different bacilli referred to as shigellae, *Shigella dysenteriae* type 1 (Shiga's bacillus) is the most virulent one[2]. Because of its emerging resistance to several antimicrobial agents[3,4], this Gram-negative pathogen poses a problem, particularly in third-world countries[5,6]. Consequently, development of a vaccine for the disease it causes has a high priority[7]. In view of the recent claim that serum antibodies to the lipopolysaccharide (LPS) of *Shigella dysenteriae* type 1 may be indicative of protection against shigellosis[8], it appeared that an understanding of the interaction between the antigenic determinant of the O-specific polysaccharide (O-SP) of this bacterium and its homologous antibodies would suggest structural criteria for an efficacious synthetic vaccine.

† Part 6 of the series Synthesis of ligands related to the O-specific antigen of *Shigella dysenteriae* type 1. For Part 5, see ref 1.

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Analysis of the LPS showed[9,10] the tetrasaccharide sequence I to be the biochemical repeating unit of the O-SP. A large number of mono- and oligo-saccharide derivatives representing various regions of the O-antigen have been synthesized[11–14]. A recent study[15] of their interaction with a monoclonal IgM permitted the identification of fragment II as an immunodeterminant of the O-SP of *Shigella dysenteriae* type 1.

3)-α-D-Glc*p*NAc-(1 → 3)-α-L-Rha*p*-(1 → 3)-α-L-Rha*p*-(1 → 2)-α-D-Gal*p*(1 →
I

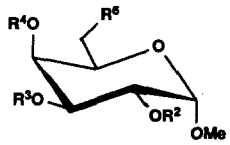
α-L-Rha*p*-(1 → 2)-α-D-Gal*p*
II

To determine the possible role of hydrogen bonding in the binding of carbohydrate antigens in several antibody systems, we have used deoxy and deoxyfluoro sugars as ligand probes[16]. A similar approach involving antibodies for the *Shigella dysenteriae* O-SP would require, inter alia, specifically deoxygenated fragments of that antigen. The main purpose of the work reported herein was the synthesis of the methyl glycosides of II deoxygenated at position 6, 3, or 4 of the galactose residue (compounds **43**, **47**, or **49** respectively). In view of the need for binding studies of the similarly modified derivatives of methyl α-D-galactopyranoside (**1**), the preparation of the deoxygenated monosaccharide units **2**, **13**, and **24** is also described.

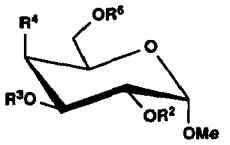
RESULTS AND DISCUSSION

Our strategy for the synthesis of the disaccharide glycosides **43**, **47**, and **49** involved coupling of the readily accessible[17] glycosyl donor **39** with each of the deoxygenated glycosyl acceptors **3**, **17**, and **29** under the conditions[18] applied[12] during the synthesis of the methyl α-glycoside of II. The galactopyranoside configuration allows selective acetalation at positions O-3 and O-4 in the absence of a free hydroxyl group at position 6, or at positions O-4 and O-6 if position 3 is not available. Thus, the unprotected glycosides **2** and **24** are suitable intermediates for the preparation of the nucleophiles **3** and **29**, respectively.

The preparation of the 4-deoxygenated glycoside **13**, needed for binding studies only, was undertaken first. Thus, following an improved procedure for the deoxygenation of carbohydrates at secondary positions[19,20], the tri-*O*-benzoyl derivative[21] **10** was treated with *N*,*N*′-thiocarbonyldiimidazole. The reaction was first conducted in toluene, as described in the β-series[22,23], giving a mixture of the 4-*O*-(imidazol-1-ylthiocarbonyl) derivative **11** (76%) and of its 3-isomer **22** (12%). The byproduct **22** resulted from the partial migration of the initially equatorially oriented benzoyl group at C-3 to the axial position at C-4. To our knowledge, such a migration was not previously observed under analogous conditions, but this phenomenon might account for the modest yield similar to that in which the β anomer **38** was previously obtained[22]. The migration of an acyl group to an axial

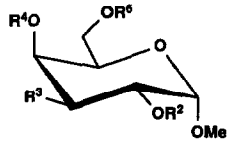


	R^2	R^3	R^4	R^6
1	H	H	H	OH
2	H	H	H	H
3	H	-CMe_2-		H
4	H	-CMe_2-		$OCMe_2OMe$
5	Bn	-CMe_2-		$OCMe_2OMe$
6	Bn	-CMe_2-		OH
7	Bn	H	H	OH
8	Bn	-CMe_2-		OBz
9	Bn	H	H	OBz



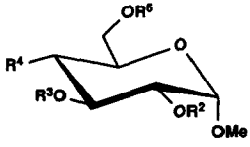
	R^2	R^3	R^4	R^6
10	Bz	Bz	OH	Bz
11	Bz	Bz	OItc	Bz
12	Bz	Bz	H	Bz
13	H	H	H	H
14	Bn	Bz	OH	Bz
15	Bn	Bz	OItc	Bz
16	Bn	Bz	H	Bz
17	H	Bz	H	Bz

Itc = imidazol-1-ylthiocarbonyl



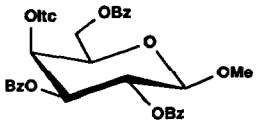
	R^2	R^3	R^4	R^6
18	H	OpMBn	H	H
19	Ac	OpMBn	Ac	Ac
20	Bz	OpMBn	Bz	Bz
21	Bz	OH	Bz	Bz
22	Bz	OItc	Bz	Bz
23	Bz	H	Bz	Bz
24	H	H	H	H
25	Bn	OpMBn	Bn	Bn
26	Bn	OH	Bn	Bn
27	Bn	OItc	Bn	Bn
28	Bn	H	Bn	Bn
29	H	H	-CHPh-	
30	CH(Ph)OMe	H	-CHPh-	

pMBn = *p*-methoxybenzyl



	R^2	R^3	R^4	R^6
31	H	H	-O-CHPh-	
32	H	Bn	-O-CHPh-	
33	Bz	Bn	-O-CHPh-	
34	Bz	Bn	OH	Bn
35	Bz	Bn	OItc	Bn
36	Bz	Bn	H	Bn
37	H	Bn	H	Bn

position from a vicinal equatorial one in pyranosides has been documented[24], and even found synthetically useful[25]. This precedent prompted us to explore the possibility of using the O-3 → O-4 benzoyl group migration for a simple preparation of the 3-deoxy derivative **23**. Since the synthetic utility of such a strategy depends on the efficiency of the conversion **10** → **21**, we conducted the thiocarbonylation in various solvents (experiments are not described). When tetrahydrofuran was used as the solvent no acyl-group migration occurred, and we applied these conditions for the high-yielding (> 95%) conversion **10** → **11**. The latter compound has been previously prepared by Rasmussen et al.[20] [mp 66-78°C; $[\alpha]_D$ + 150.2° (*c* 2.0, $CHCl_3$)], whereas we found mp 90-92°C (EtOH); $[\alpha]_D$ + 153° (*c* 1.7, $CHCl_3$), indicating that the compound is polymorphous. Deoxygenation of **11** with tributyltin hydride in the presence of a catalytic amount of 2,2′-azobis-(2-methylpropionitrile)[26] produced the crystalline deoxy glycoside **12** as the only product. The target **13** was obtained from **12** upon Zemplén debenzoylation.



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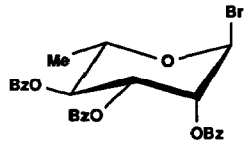

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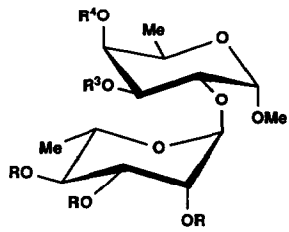
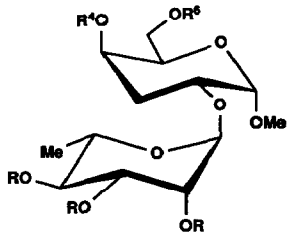
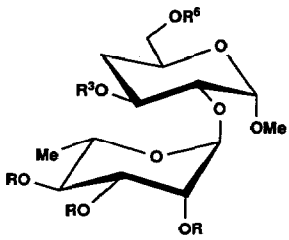


	R	R^3	R^4
40	Bz	$-CMe_2-$	
41	Bz	H	H
42	H	$-CMe_2-$	
43	H	H	H



	R	R^4	R^6
44	Bz	-CHPh-	
45	Bz	H	H
46	H	-CHPh-	
47	H	H	H



	R	R^3	R^6
48	Bz	Bz	Bz
49	H	H	H

When **10** was treated with *N,N'*-thiocarbonyldiimidazole in the boiling solvents dichloroethane, 1,2-dimethoxyethane, pyridine, *N,N'*-dimethylformamide (DMF), toluene, xylene, and mesitylene, the migration product **22** was present in the crude mixtures in amounts of 6, 6, 8, 13, 16, 33, and 50%, respectively, as determined by ^{1}H NMR spectroscopy. Some decomposition of the carbohydrate components during this attempted one-pot conversion of **10** into **22** was also observed. Therefore, a two-step procedure was considered. Quantitative conversion of **10** into **21** was not achieved by heating either alone or in the presence of imidazole as catalyst. Treatment[25] of **10** with silver oxide in DMF and separation of the crude product mixture by chromatography afforded the hitherto unknown **21** in only 44% yield, which did not improve by heating with silver oxide in either DMF or mesitylene (not described in the Experimental). As these results were not satisfactory, another approach to **24** was designed.

Selective protection at position 3 of **1** via stannylation, with tetrabutylammonium iodide as an activator[27,28], afforded methyl 3-*O*-*p*-methoxybenzyl-α-D-galactopyranoside (**18**) in a yield of 60%. The position of the *p*-methoxybenzyl group followed clearly from the ^{1}H NMR spectrum of the conventionally prepared per-*O*-acetyl derivative **19**. The regioselectivity of *p*-methoxybenzylation could not be improved by performing the reaction in toluene or acetonitrile, or in the presence of cesium fluoride and potassium iodide in DMF[12,29]. The *p*-methoxybenzyl moiety was chosen as a protective group because it can be selectively removed[30,31] in the presence of either ester or ether functions, thus allowing more flexibility in further blocking strategy. Benzoylation of **18** afforded **20** which was converted into **21** in 94% overall yield using ceric ammonium nitrate[30] (CAN). In an alternative way to a partially protected derivative of methyl α-D-galactopyranoside having HO-3 free, compound **18** was fully benzylated[32] to give **25**, and this, upon selective removal of the *p*-methoxybenzyl group, was converted into the tribenzyl ether **26** (92%).

Treatment of **21** with *N*,*N*′-thiocarbonyldiimidazole in refluxing tetrahydrofuran gave **22** in theoretical yield. Deoxygenation of **22**, conducted as described for the conversion **11** → **12**, afforded the known[33] **23** in 88% yield, together with two more polar byproducts, the less polar of which was identified as the precursor **21**. A comparison of the two-step deoxygenation conducted with the tri-*O*-benzyl (**26**) and the tri-*O*-benzoyl (**21**) derivatives showed the importance of the choice of protective groups for this transformation. The conversion of **26** into the 4-*O*-(imidazol-1-ylthiocarbonyl) derivative **27**, although a slow process, went smoothly. However, byproducts were formed upon radical deoxygenation of **27**. The main one (21%) resulted from the loss of the imidazol-1-ylthiocarbonyl moiety, regenerating the starting derivative **26**. Owing to the formation of byproducts, the yield of the target compound **28** was modest (63%). The pathway involving the tri-*O*-benzoylated precursor **21** was definitely preferred. The sequence **20** → **21** → **22** → **23** could be performed without purification of intermediates, and the overall yield of **23** was 87%. The isolated **23** was then deprotected to give the desired deoxy derivative **24** in theoretical yield.

To obtain the 3-deoxygenated glycosyl acceptor, compound **24** was treated with benzaldehyde dimethyl acetal, to afford the benzylidene derivative **29**. In this connection, it is interesting to note the high nucleophilicity of HO-2 in **24**. It reacted with the dimethyl acetal easily, and with prolonged reaction time the fully protected mixed acetal **30** was formed, in almost theoretical yield, as seen by mass and NMR spectroscopy. The material was isolated as a 1:1 mixture of diastereoisomers at C-2′. Unwanted **30** could be converted in situ to **29** by mild hydrolysis (see Experimental).

D-Fucose was converted to the 6-deoxygenated ligand **2** (55%) via methyl glycosylation[34]. Isopropylidenation[35] then gave the required nucleophile **3** in a virtually theoretical yield. Compound **3** and its L enantiomer were formed on several occasions[36–40] as synthetic intermediates, but were never crystallized. Our

preparation solidified upon standing (as did the L enantiomer once before[38]) and, in spite of its low melting point (38–39°C), it could be readily recrystallized from hexane–pentane and has now been fully characterized.

The synthesis of the glycosyl acceptor **17**, deoxygenated at position 4, and open to the construction of a (1 → 2)-linkage, was pursued starting with compounds having either the D-*gluco* or D-*galacto* configuration. In the first approach, commercially available methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**31**) was mono-*O*-benzylated[41] to give **32**, benzoylation of which afforded **33**. Subsequent reductive cleavage[42] of the 4,6-*O*-benzylidene ring in **33** liberated the HO-4 to give the appropriately blocked precursor **34**. Activation of **34** via the 4-*O*-(imidazol-1-ylthiocarbonyl) group (→ **35**) and subsequent deoxygenation according to Barton furnished **36** together with a few byproducts, the major one of which, **34** (11%), resulted from the loss of the activating group.

Analysis of the deoxygenation reactions **10** → **12**, **21** → **23**, **26** → **28**, and **34** → **36**, allows two conclusions. First, when axial positions are activated via the imidazol-1-ylthiocarbonyl function, radical deoxygenation can be performed more selectively than in the case of the equatorial counterparts. The importance of the thiocarbonyl group in a similar situation[43] has already been documented. Second, since benzyl groups, especially when at a primary position, are somewhat prone to undergo cleavage during the deoxygenation step[43], the use of substrates protected with the less labile benzoyl groups is preferred for this type of conversion. In view of this, a new route to the required methyl 4-deoxy-α-D-galactopyranoside bearing a free hydroxyl group at position 2 has been designed.

In keeping with a previously described strategy[35,44] compound **1** was treated with 2,2-dimethoxypropane to give compound[45] **4** (69%). Benzylation of **4** afforded **5**, which was treated at 80°C with aqueous acetic acid to give **7**. Selective di-*O*-benzoylation of **7** produced the alcohol **14** (72%). The yield of **14** could not be improved via an alternate pathway, involving successively, selective deprotection of **5** to give compound[46] **6**, benzoylation (→ **8**), deacetalation (→ **9**), and selective monobenzoylation of equatorial HO-3. Treatment of **14** with *N*,*N*′-thiocarbonyldiimidazole in refluxing tetrahydrofuran gave the axial substitution product **15** (96%), exclusively. The latter was then smoothly deoxygenated to **16** (94%), hydrogenolysis of which afforded the desired methyl 3,6-di-*O*-benzoyl-4-deoxy-α-D-*xylo*-hexopyranoside (**17**).

Condensation of the glycosyl acceptors **3**, **17**, and **29**, respectively, with 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide (**39**) was achieved under base-deficient conditions using silver trifluoromethanesulfonate as the promotor and *sym*-collidine as the acid scavenger[18]. The benzylidene group was previously[12] found to be stable under such conditions, but to assure retention of the isopropylidene group in **3**, the reaction was initiated at −25°C, and *sym*-collidine was added dropwise, so as to keep the solution neutral. Under such conditions the α-(1 → 2)-linked disaccharides **40**, **44**, and **48** were isolated in excellent yield (> 90%). Deacetalation of **40** was achieved with aqueous acetic acid (→ **41**), and subsequent deben-

zoylation afforded the crystalline **43**. We find this route to **43** more convenient than one having the deprotection steps in reverse order. Zemplén debenzoylation of **48** to give **49** was straightforward. Compound **47** could be obtained from **44** via either one of two sequences, namely debenzylidenation via hydrogenolysis (→ **45**) followed by debenzoylation (Zemplén), or initial debenzoylation (→ **46**) and subsequent deacetalation. We examined both possibilities, and found the former route to be superior, since it involved only one chromatography step.

EXPERIMENTAL

General Methods.—Melting points were determined on a Kofler hot stage. Optical rotations were measured at 25°C, on a Perkin–Elmer automatic polarimeter, Model 241 MC. All reactions were monitored by thin-layer chromatography on precoated slides of Silica Gel G F254 (Analtech). Detection was effected by charring with 5% H_2SO_4 in EtOH and, when applicable, by examination with UV light. Preparative chromatography was performed by elution from columns of Silica Gel 60 (particle size 0.04–0.063 mm). Unless stated otherwise, NMR data (Tables I–III) were extracted from spectra measured for solutions in $CDCl_3$ at room temperature, on a Varian Gemini spectrometer operating at 300 MHz for ^1H and at 75 MHz for ^{13}C. Chemical shifts (δ, ppm) were measured using Me_4Si as the internal standard. Proton-signal assignments were made by first-order analysis of the spectra, and were supported by homonuclear decoupling. Of the two magnetically nonequivalent geminal protons at C-6, the one resonating at lower field is denoted Ha and the one at higher field Hb. For the compounds deoxygenated at C-4 and C-3, the axial proton is denoted H*ax* and the equatorial one H*eq*. Carbon-signal assignments were routinely made by mutual comparison of the spectra and, when feasible, by HETCOR experiments. In entries for disaccharides in Tables I–III, the data in the second row, if present, refer to the rhamnosyl residue. Reactions requiring anhydrous conditions were performed under N_2 or Ar using common laboratory glassware, reagents and solvents being handled with gas-tight syringes. Solutions in organic solvents were dried with anhydrous sodium sulfate, and concentrated at 2 kPa/40°C. 2,2′-Azobis(2-methylpropionitrile) (99%, Eastman Kodak Company) was used as supplied. D-Fucose, methyl α-D-galactopyranoside monohydrate, and methyl 4,6-*O*-benzylidene-α-D-glucopyranoside, purchased from Sigma Chemical Company, were used as supplied.

Methyl 2,3,6-tri-O-benzoyl-4-O-(imidazol-1-ylthiocarbonyl)-α-D-galactopyranoside (**11**).—(*a*) A mixture of methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside[21] **10** (5.06 g, 10 mmol) and *N,N′*-thiocarbonyldiimidazole (2.85 g, 16 mmol) in toluene (150 mL) was refluxed overnight and concentrated. A solution of the residue in CH_2Cl_2 was washed successively with 5% HCl and water, dried, concentrated in vacuo, and chromatographed (9:1 toluene–EtOAc) to give first **22** (740 mg, 12%), identical with the material described below.

TABLE I

^{13}C NMR Chemical shifts (δ) [a]

Compound	C-1	C-2	C-3	C-4	C-5	C-6	OCH_3	OCH_2Ph OCH_2pMPh	CH_2PhOCH_3 $OCHPh$
3 [b,c]	98.58	69.49	76.21	75.66	63.72	16.35	55.45		
4 [d]	98.35	69.06 [e]	76.20 [f]	73.31 [f]	67.44 [e]	60.33	55.27		
5 [g]	98.18	76.14 [e]	76.28 [e]	73.78	66.61	60.35	55.36	72.34	
6 [b,h]	98.34	76.06	76.25	74.58	67.09	62.81	55.54	72.37	
7 [b]	97.82	76.56	69.02 [e]	70.44	68.93 [e]	63.16	55.42	72.92	
8 [b,i]	98.25	76.04 [e]	76.10 [e]	75.52	65.49	64.06	55.44	72.98	
9	97.75	76.57	67.58 [e]	68.94 [e]	68.89 [e]	63.66	55.31		
11 [j]	97.58	68.09 [e]	69.06 [e]	77.53	66.48 [e]	61.96	55.96		
14 [b]	98.37	73.39	72.55	68.06	67.48	63.39	55.46	73.17	
15 [b]	98.48	73.37 [f]	69.85	78.05	66.43	62.05	55.93	73.28 [f]	
16 [b]	98.62	77.56	70.41	33.24	65.23	66.19	55.30	72.91	
17	100.01	71.66 [f]	71.51 [f]	32.76	65.75	66.11	55.37		
18	99.52	69.34 [e]	77.76	68.45 [e]	68.24 [e]	63.07	56.45 [f]	71.85	55.32 [f]
19 [k]	97.28	70.07	72.81	67.40	66.51	62.47	55.39	71.54	
20 [b]	97.52	70.77	72.57	68.12	66.90	63.22	55.50	71.15	55.21
21 [b]	97.56	72.13	67.05	71.48	67.05	62.98	55.65		
22	97.65	68.18 [e]	76.48	68.67 [c]	66.80 [c]	62.45	55.87		
25 [b,l]	98.77	76.38	78.85	75.19	69.23	69.13	55.36		55.29
26 [b]	97.92	77.37	70.27	76.95	69.06	69.02	55.41	75.13, 73.46, 72.98	
27	98.01	73.71 [c]	80.68	73.82 [c]	68.26	68.00	55.52	74.93, 73.52, 72.88	
28 [b]	97.68	71.06	27.49	73.14	69.11	69.45	55.12	73.41, 71.25, 71.14	
29 [b]	99.71	63.72	32.69	73.37	61.84	69.55	55.45		101.02
33	97.87	73.57	75.79	82.21	62.33	69.00	55.41	74.75	101.32
33 [b,m]	98.70	74.32	76.43	83.12	63.20	69.45	55.31	101.99, 75.12	
34 [b]	97.24	73.87	79.66	71.52	69.78	69.78	55.31	75.17, 73.67	
34 [b,m]	97.71	74.40	80.13	72.71	70.76	70.85	54.99	75.23, 73.77	
35	96.96	73.79	76.77	79.05	68.24	69.05	55.68	74.98, 73.85	
36 [b]	97.82	75.05	72.77	33.92	66.79	72.38	55.22	73.49, 71.77	
37 [b]	99.89	73.21	75.92	32.90	67.14	72.37	55.18	71.47, 73.41	
40 [b,n]	98.96	77.21	75.16	76.21	62.96	17.88	55.51		
	98.36	70.87	69.75	72.06	66.99	16.39			
41 [b]	99.11	78.76	68.83	72.07	65.31	17.85	55.03		
	99.74	70.78	70.19	71.75	67.11	16.12			
42 [o]	99.02	76.52 [e]	75.29	76.21 [e]	62.68	17.69 [f]	55.37		
	101.10	70.76 [f]	71.37 [f]	72.63	68.44	16.27 [f]			
43 [b,p]	99.85	78.09	70.98 [f]	72.80 [f]	67.30	17.71 [f]	55.82		
	103.80	70.13	71.06 [f]	72.83 [f]	69.58	16.18 [f]			
44 [b]	99.10	73.10 [c]	29.80	73.40 [c]	61.70	69.60	55.20		101.00
	98.30	71.20	69.80	72.00	67.00	17.90			
45 [b]	99.00	73.17	32.00	68.91	68.57	64.02	55.04		
	98.42	71.19	69.81	71.93	67.03	17.83			
46	101.20	73.42 [f]	29.60	73.66 [f]	61.71	69.61	55.24		99.19 [e]
	99.22	71.16 [e]	71.61 [e]	71.61 [e]	68.09	17.73			
47 [b,p]	99.22	71.96	31.96	66.89	71.58	62.43	55.54		
	101.22	71.39	71.15	72.96	70.02	17.74			
48 [b]	99.49	79.89	69.72	33.31	65.23	66.09	55.24		
	99.57	71.03	69.41	71.92	67.23	17.79			
49 [b,p]	103.71	82.92	67.12 [f]	34.24	67.06 [f]	64.58	55.61		
	100.24	70.11	71.07	72.91	69.29	17.78			

Further elution gave **11** (4.68 g, 76%), mp 90–92°C (EtOH); $[\alpha]_D$ + 129° (*c* 1.0, $CHCl_3$), CIMS; *m/z* 617 ($[M + H]^+$). Anal. Calcd for $C_{32}H_{28}N_2O_9S$: C, 62.22; H, 4.73; N, 4.54; S, 5.19. Found: C, 62.16; H, 4.67; N, 4.54; S, 5.27.

(*b*) A mixture of **10** (506 mg, 1 mmol) and *N,N'*-thiocarbonyldiimidazole (356 mg, 2 mmol) in THF (5 mL) was refluxed for 2 h. Workup, as described above, followed by chromatography afforded **11** in virtually theoretical yield.

*Methyl 2,3,6-tri-*O*-benzoyl-4-deoxy-α-*D*-xylo-hexopyranoside* (**12**) *and methyl 4-deoxy-α-*D*-xylo-hexopyranoside* (**13**).—To a refluxing solution of tributyltin hydride (1.74 mL, 6.48 mmol) and 2,2'-azobis(2-methylpropionitrile) (15 mg, 0.54 mmol) in toluene (180 mL) was added dropwise a solution of **11** (2.2 g, 3.6 mmol) in toluene (75 mL), and the mixture was stirred at 110°C for 1 h. Concentration and chromatography (toluene–EtOAc, gradient) of the residue gave **12** (1.73 g, 98%), mp 120–121°C (from EtOH); $[\alpha]_D$ + 126° (*c* 0.9, $CHCl_3$); lit.[19] mp 116–117°C; $[\alpha]_D$ + 132.6° (*c* 2.0, $CHCl_3$);

Debenzoylation (Zemplén) of **12** gave **13** (95%), mp 92–93°C (lit.[47] mp 90–91°C).

*Methyl 3-*O*-p-methoxybenzyl-α-*D*-galactopyranoside* (**18**).—A suspension of methyl α-D-galactopyranoside (4.85 g, 25 mmol) and dibutyltin oxide (6.21 g, 25 mmol) in toluene (350 mL) was heated for 3 at 160°C (bath), in a Soxhlet apparatus containing 3A molecular sieves. The solution was concentrated, the residue was dissolved in dioxane (300 mL), and tetrabutylammonium iodide (10.2 g, 27.5 mmol) was added, followed by dropwise addition of *p*-methoxybenzyl chloride (3.7 mL, 27.5 mmol). The mixture was stirred overnight at 90°C, at which time little of the starting material remained, as seen by TLC (9 : 1 $CHCl_3$–MeOH). After concentration, chromatography (25 : 1 $CHCl_3$–MeOH) afforded the main product **18** (4.71 g, 60%), mp 116–117°C (from EtOAc); $[\alpha]_D$ + 132° (*c* 1.0, $CHCl_3$); CIMS: *m/z* 332 ($[M + NH_4]^+$). Anal. Calcd for $C_{15}H_{22}O_7$: C, 57.32; H, 7.05. Found: C, 57.35; H, 7.00.

*Methyl 2,4,6-tri-*O*-acetyl-3-*O*-p-methoxybenzyl-α-*D*-galactopyranoside* (**19**).—Acetic anhydride (1 mL, 10.6 mmol) was slowly added to a solution of **18** (315 mg, 1 mmol) in pyridine (6 mL) and the mixture was stirred overnight at room temperature. After concentration, the residue was chromatographed (9 : 1 toluene–acetone) to give **19** in theoretical yield, mp 125–126°C (from MeOH); $[\alpha]_D$ + 137° (*c* 1.0, $CHCl_3$); CIMS: *m/z* 458 ($[M + NH_4]^+$). Anal. Calcd for $C_{21}H_{28}O_{10}$: C, 57.26; H, 6.40. Found: C, 57.26; H, 6.39.

Notes to Table I:

[a] Data in the second row when present are for the rhamnosyl residue. [b] Chemical shift assignments were made by HETCOR. [c] δ_{OCMe_2} 109.13, δ_{OCMe_2} 27.90, 26.03. [d] δ_{OCMe_2} 109.40, 100.05, δ_{OCMe_2} 27.84, 25.99, 24.52, 24.44. [e] These assignments may be interchanged. [f] These assignments may be reversed. [g] δ_{OMe} 48.56; δ_{OCMe_2} 109.01, 100.05; δ_{OCMe_2} 28.22, 26.43, 24.53, 24.40. [h] δ_{OCMe_2} 109.43, δ_{OCMe_2} 28.08, 26.43. [i] δ_{OCMe_2} 109.50, δ_{OCMe_2} 28.03, 26.37. [j] $\delta_{C=S}$ 183.38. [k] δ_{OCOCH_3} 21.06, 20.91, 20.84. [l] $\delta_{OCH_2Ph,\ OCH_2PhOCH_3}$ 74.69, 73,56, 73.46, 72.95. [m] Spectrum was obtained in benzene-d_6 using Me_4Si as an internal standard. [n] δ_{OCMe_2} 108.95; δ_{OCMe_2} 26.48, 28.46. [o] δ_{OCMe_2} 108.88; δ_{OCMe_2} 28.31, 26.38. [p] Spectrum was obtained in D_2O using methanol-d_4 as an internal standard (δ 49.00 ppm).

TABLE II

^{1}H NMR Chemical shifts (δ) [a,b]

Compound	H-1	H-2	H-3*ax*	H-3*eq*	H-4*eq*	H-4*ax*	H-5	H-6a	H-6b	OCH_3	OCH_2Ph [c] ($PhOCH_3$) CHPh
3	4.72d	3.79dd	4.19t		4.05dd		4.13dq	1.33d [d]	1.33d [d]	3.44s	
4	4.73d	3.77m	4.17m		4.17m		4.03bt	3.64dd	3.58dd	3.42, 3.19	
5	4.66d	3.50dd	4.33dd		4.19dd		4.04ddd	3.68dd	3.51dd	3.39, 3.21	4.82, 4.71
6	4.70d	3.52dd	4.38dd		4.23dd		4.02m	3.93ddd	3.82ddd	3.39s	4.82, 4.72
7	4.74d	3.74dd	3.97m [d]		4.08d		3.91m [d]	3.80m	3.80m	3.36s	4.68s
8	4.69d	3.55dd	4.38dd		4.28m		4.28m	4.55m	4.55m	3.38s	4.82, 4.77
9	4.72d	3.75dd	4.05m		4.05m		4.08t	4.94dd	4.59dd	3.35s	4.68s
11	5.32d	5.59dd	6.04dd		6.63d		4.67t	4.58dd	4.39dd	3.51s	
14	4.84d	4.15dd	5.55dd		4.32bs		4.26bt	4.59dd	4.50dd	3.46s	
15	4.93d	4.02dd	5.82dd		6.51d		4.53m	4.53m	4.30dd	3.51s	
16	4.84d	3.70dd	5.58ddd		2.38ddd	1.67q	4.28m	4.40dd	4.32dd	3.45s	
17	4.92d	3.79ddd	5.39ddd		2.28ddd	1.74q	4.25m	4.43dd	4.38dd	3.48s	
18	4.84d	3.97ddd [d]	3.61dd		4.04bd		3.76m	3.93m [d]	3.80m	3.42s	4.67, 4.62 (3.80s)
19 [e]	4.97d	5.06dd	3.90dd		5.54bd		4.13m	4.13m	4.13m	3.39s	4.62, 4.39 (3.80s)
20	5.23d	5.43dd	4.19dd		5.95bd		4.47m	4.47m	4.47m	3.39s	4.69, 4.50 (3.75s)
21	5.20d	5.40dd	4.50m [d]		5.82d		4.50m [e]	4.50m [d]	4.50m [d]	3.44s	
21 [f]	5.21d	5.68dd	4.34m		5.73d		4.12dd	4.61dd	4.41dd	3.00s	
22	5.31d	5.83dd	6.45dd		6.14d		4.63m [d]	4.63m [d]	4.43dd	3.52s	
25	4.67d	4.01dd	3.91dd		3.89m [d]		3.88m [d]	3.50d	3.50d	3.36s	[g] (3.80s)
26	4.69d	3.79dd	3.99ddd		3.92d		3.94bt	3.56d	3.56d	3.33s	[h]
26 [d]	4.74d	3.97dd	4.22m [d]		3.85bd		4.04bt	4.71dd	3.69dd	3.22s	[i]
27	4.80d	4.20dd	5.86dd		4.33bd		4.08bt	3.64dd	3.56dd	3.40s	[j]
28	4.75d	3.87dbt	1.85dt	2.12ddd	3.96bs		3.69dt	3.62dd	3.57dd	3.42s	[k]
29	4.82d	4.11m [d]	1.92ddd	2.16dbt	4.11m [d]		3.58bs	4.24d	4.07dd	3.48s	5.50s
33	5.07d	5.11dd	4.20t		4.33dd		3.86m [d]	3.86m [d]	3.86m [d]	3.37s	4.88, 4.77 5.62s
33 [f]	5.05d	5.46dd	4.37t		3.59t		3.92ddd	4.12dd	3.49t	2.89s	4.92, 4.79 5.33s

34	5.05d	5.08dd	4.02bt		3.77m		3.77m	3.77m	3.77m	3.38s	
34 [f]	5.12d	5.43dd	4.25dd		3.77t		4.00m	3.67d [d]	3.67d [d]	3.02s	4.86, 4.77 4.38 [d], 4.34 [d]
35	5.15d	5.24dd	4.35t		6.01t		4.10ddd	3.67dd	3.58dd	3.45s	4.74, 4.53 4.51, 4.46
36	5.08m [d]	5.07m [d]	4.10m		2.20ddd	1.65q	4.02m	3.58dd	3.51dd	3.36s	4.66, 4.60 4.59s
37	4.85d	3.63m	3.72ddd		2.09ddd	1.47q	3.93m	3.88dd	3.53dd	3.42s	4.62, 4.69 4.57s
40	4.84d	3.84d	4.38dd		4.10m [d]		4.10m [d]	1.38d		3.46s	[l]
	5.32d	5.79dd	5.91dd		5.64t		5.64t	1.35d			
41	4.95d	4.03dd [d]	4.16dd		3.90bd		3.98m [d]	1.31d [m]		3.42s	
	5.29bs	5.88bs	5.93dd		5.68t		4.43m	1.36d [m]			
43 [o]	4.83d	3.77m [d]	3.87dd		3.77m [d]		4.04m	1.22d		3.40s	
	4.91s	4.03bs	3.77m [d]		3.44t		3.69m	1.29d			
44	5.03d	4.21m	2.24m [d]	2.24m	4.21m [d]		3.66bs	4.26bd	4.10dd	3.52s	5.55s
	5.14d	5.63dd	5.88dd		5.65t		4.35m	1.35d			
45	4.98d	4.23m	2.13m	2.13m	4.19m		3.78dt	3.92bs		3.48s	
	5.15d	5.63dd	5.87d		5.66t		4.36m	1.35d			
47 [o]	4.82d	3.98m [d]	2.01ddd	1.87ddd	3.98m [d]		3.78bt	3.66m [d]	3.66m [d]	3.42s [d]	
	4.85s	3.88dd	3.70dd		3.39t [d]		3.66m [d]	1.26d			
48	5.06d	3.98dd	5.57dd		2.54ddd	1.74q	4.35m	4.42m [d]	4.44m [d]	3.52s	
	5.30d	5.51dd	5.85dd		5.64t		4.35m	1.33d			
49 [o]	4.92d	5.30dd [d]	3.97ddd [d]		2.00ddd	1.489	3.90m [d]	3.65dd	3.58dd	3.41s [d]	
	4.93d	4.06dd	3.77dd		3.45t [d]		3.72m [d]	1.30d			

[a] Data in the second row when present are for the rhamnosyl residue. [b] Peak multiplicities: d, doublet; m, multiplet; q, quartet; s, singlet; t, triplet; b, broad. [c] Benzyl methylene protons signals are doublets unless stated otherwise. [d] Overlapping signals. [e] δ_{OCOCH_3} 2.14, 2.10, 2.08. [f] Spectrum was obtained in benzene-d_6 using Me_4Si as an internal standard. [g] δ_{CH_2Ph} 4.93, 4.55; 4.83, 4.68; 4.76, 4.66; 4.47, 4.38. [h] δ_{CH_2Ph} 4.81, 4.61; 4.70, 4.43; 4.65, 4.52. [i] δ_{CH_2Ph} 45.01, 4.60; 4.33, 4.26; 4.30. [j] δ_{CH_2Ph} 4.59; 4.54, 4.76; 4.50, 4.31. [k] δ_{CH_2Ph} 4.56; 4.55, 4.45; 4.51, 4.34. [l] $\delta_{OC(CH_3)_2}$ 1.54s, 1.36s. [m] These two assignments may be reversed. [o] Spectrum was obtained in D_2O using HOD as an internal standard (δ 4.78 ppm, s).

Methyl 2,4,6-tri-O-benzoyl-3-O-p-methoxybenzyl-α-D-galactopyranoside (**20**).—Benzoyl chloride (420 μL, 3.6 mmol) was added at 0°C to a solution of **18** (315 mg, 1 mmol) in pyridine (5 mL), and the mixture was stirred overnight at room temperature. After usual workup the crude product was chromatographed (5:1 toluene–EtOAc) to yield glassy **20** (613 mg, 98%); $[\alpha]_D + 85°$ (*c* 1.4, $CHCl_3$); CIMS: *m/z* 644 ($[M + NH_4]^+$). Anal. Calcd for $C_{36}H_{34}O_{10}$: C, 69.00; H, 5.47. Found: C, 69.08; H, 5.48.

Methyl 2,4,6-tri-O-benzoyl-α-D-galactopyranoside (**21**)—(*a*) A suspension of **10** (4.1 g, 8.1 mmol) and silver oxide (9.5 g, 41.1 mmol) in DMF (260 mL) was stirred in the dark at room temperature for 48 h. TLC (9:1 toluene–acetone) showed that the reaction was essentially complete, and that the conversion **10** → **21** was ~ 50%. The mixture was filtered through Celite, the filtrate was concentrated, and the residue was chromatographed (20:1 toluene–acetone). Eluted first was the unchanged **10** (2 g, 49%).

Further elution gave amorphous **21** (1.78 g, 44%); $[\alpha]_D + 104°$ (*c* 1.0, $CHCl_3$); CIMS: *m/z* 524 ($[M + NH_4]^+$), 507 ($[M + H]^+$). Anal. Calcd for $C_{28}H_{26}O_9$: C, 66.40; H, 5.17. Found C, 66.37; H, 5.23.

(*b*) Ceric ammonium nitrate (9.98 g, 18.2 mmol) was added portionwise to a solution of **20** (5.43 g, 8.67 mmol) in a mixture of 4:1 MeCN–water (115 mL), each fresh portion of the reagent being added when the developed orange color had disappeared. The mixture was kept at 25°C for an additional hour. A sole product was formed, as seen by TLC. After addition of EtOAc (200 mL), the mixture was washed with water, dried, and concentrated. The residue was chromatographed (92:8 toluene–EtOAc) to give **21** (4.12 g, 94%).

Methyl 2,4,6-tri-O-benzoyl-3-O-(imidazol-1-ylthiocarbonyl-α-D-galactopyranoside (**22**).—Compound **21** (3.92 g, 7.74 mmol) was treated as described for the preparation of **11** (*b*), to afford **22** as a single product. Chromatography (9:1 toluene–EtOAc) gave amorphous **22** (4.62 g, 97%), $[\alpha]_D + 128°$ (*c* 1, $CHCl_3$); CIMS: *m/z* 617 ($[M + H]^+$). Anal. Calcd for $C_{32}H_{28}N_2O_9S$: C, 62.22; H, 4.73; N, 4.54; S, 5.19. Found: C, 62.33; H, 4.70; N, 4.51; S, 5.23.

Methyl 2,4,6-tri-O-benzoyl-3-deoxy-α-D-xylo-hexopyranoside (**23**).—Treatment of **22** (4.62 g, 7.5 mmol) with tributyltin hydride (3.6 mL, 13.6 mmol) and 2,2′-azobis(2-methylpropionitrile) (180 mg, 1.1 mmol), as described for the preparation of **12**, gave **23** as a white foam (3.23 g, 88%); $[\alpha]_D + 71°$ (*c* 0.5, $CHCl_3$); lit.[48] $[\alpha]_D + 43.9°$ (*c* 0.6, $CHCl_3$); CIMS: *m/z* 508 ($[M + NH_4]^+$), 491 ($[M + H]^+$); the NMR characteristics are consistent with those reported[48]. Anal. Calcd for $C_{28}H_{26}O_8$: C, 68.56; H, 5.34. Found: C, 68.56; H, 5.38.

Debenzoylation (Zemplén) of **23** (2.9 g, 5.9 mmol) afforded **24** (945 mg, 96%); mp 164–165°C (lit.[49] mp 163–164°C).

Methyl 4,6-O-benzylidene-3-deoxy-α-D-xylo-hexopyranoside (**29**) *and methyl 4,6-O-benzylidene-3-deoxy-2-O-(α-methoxybenzyl)-α-D-xylo-hexopyranoside* (**30**).—Compound **24** (867 mg, 4.87 mmol) was treated, at room temperature for 30 min, with benzaldehyde dimethyl acetal (7.5 mL) in the presence of a catalytic amount of

TABLE III

^{1}H NMR Coupling Constants (Hz)

Compound	$J_{1,2}$	$J_{2,3ax}$; $J_{2,3eq}$	$J_{3ax,3eq}$	$J_{3,4eq}$; $J_{3,4ax}$ $J_{3ax,4}$; $J_{3eq,4}$	$J_{4ax,4eq}$	$J_{4eq,5}$; $J_{4ax,5}$	$J_{5,6a}$; $J_{5,6b}$	$J_{6a,6b}$	$J_{Ha,Hb}$ (OCH_2Ph)
3	3.9	6.6		6.1		2.3	6.6		
4	3.9	[a]		[a]		<1	5.4, 7.1	10.0	
5	3.5	7.8		5.4		2.4	5.5, 7.0	9.8	12.6
6	3.4	7.8		5.6		2.7	6.0, 4.2	11.7	12.6
7	3.6	9.7		2.8		<1	5.2, [a]	[a]	
8	3.6	7.8		5.5		2.3	[a]	11.6	12.5
9	3.5	9.4		[a]		<1	7.2, 5.5	11.3	
11	3.6	10.9		3.2		<1	6.4, 6.3	11.2	
14	3.6	10.4		3.2		<1	6.0, 6.8	11.4	12.3
15	3.5	10.5		3.1		<1	5.9, [a]	11.0	12.3
16	3.4	9.8		5.1, 11.3	12.5	1.8, 11.7	6.2, 3.7	11.4	12.5
17	3.7	10.2		5.1, 11.2	12.6	2.0, 11.9	6.1, 3.9	11.5	
18	3.9	9.8		3.4		<1	1.7, [a]	[a]	
19	3.7	10.5		3.4		<1	[a]	[a]	11.2
20	3.7	10.5		3.3		<1	[a]	[a]	11.9
21	3.6	10.4		3.4		<1	[a]	[a]	
21 [b]	3.5	10.5		3.8		<1	5.6, 6.1	11.4	
22	3.6	10.7		3.3		<1	7.1, 8.8	14.2	
25	3.2	10.5		2.7		<1	6.4		11.5, 12.2 11.2, 11.8
26	3.7	10.0		3.7		<1	6.4		11.6, 11.9 11.2
26 [b]	3.4	10.2		3.5		<1	6.4, 6.6	9.3	11.5, 12.0 [a]
27	3.4	10.3		3.1		<1	7.3, 5.9	9.3	11.9, 11.7 11.8
28	3.2	11.3, 4.3	13.2	2.6, 1.8		1.4	6.3, 6.5	9.6	11.7, 12.0 12.0
29	3.4	12.2, 6.7	12.6	3.2, 5.2		<1	[a], 1.7	12.3	
33	3.8	9.3		9.8		4.4	[a], 6.4	9.3	11.8
33 [b]	3.7	9.6		9.4		9.4	4.9, 10.3		12.2
34	3.6	9.5		8.5		[a]	[a]		11.5, 12.0
34 [b]	3.6	9.9		8.8		9.5	4.4, 4.4		11.6, 12.4
35	3.6	9.5		9.8		10.0	3.6, 4.8	10.6	11.7, 11.7
36	[a]	[a]		5.1, 11.9	12.9	2.1, 11.9	5.6, 4.6	10.1	12.1
37	3.7	9.3		4.7, 10.8	12.7	2.2, 12.0	5.4, 4.6	10.2	11.7
40	3.4	8.0		5.3		2.7	5.5		
	1.7	3.3		10.2		9.9	6.5		
41	3.3	9.9		3.0		<1	6.6		
	<1	3.3		10.0		9.7	6.2		
43	3.6	10.3		3.2		<1	6.5		
	<1	[a]		9.7		9.7	6.2		
44	3.1	11.2 [a]	13.2	3.3, [a]		<1	1.6, 6.2	12.5	
	1.5	3.5		10.1		10.0	<1		
45	3.2	[a], 6.4	[a]	[a], 3.3		3.5	5.0, [a]	[a]	
	1.7	3.3		10.3		9.8	6.2		
47 [c]	3.4	11.3, 3.7 [d]	13.4	4.1 [d], 2.7		<1	7.1 [d], 4.9 [d]		[a]
	<1	3.4		9.7		[a]	6.3		
48	3.4	10.0		5.1, 11.9	12.2	2.2, 11.9	6.2, 3.9	11.6	
	1.7	3.4		10.0		10.0	6.3		

TABLE III (continued)

Compound	$J_{1,2}$	$J_{2,3ax}$; $J_{2,3eq}$	$J_{3ax,3eq}$	$J_{3,4eq}$; $J_{3,4ax}$ $J_{3ax,4}$; $J_{3eq,4}$	$J_{4ax,4eq}$	$J_{4eq,5}$; $J_{4ax,5}$	$J_{5,6a}$; $J_{5,6b}$	$J_{6a,6b}$	$J_{Ha,Hb}$ (OCH_2Ph)
49 [c]	3.7	9.7		5.2, 11.9	11.9	2.1, 11,9	[a], 6.3	12.0	
	1.6	3.4		9.8		9.7	6.3		

[a] Coupling constant could not be determined. [b] Spectrum was obtained in benzene-d_6 with Me_4Si as an internal reference. [c] Spectrum was measured in D_2O with methanol-d_4 as internal reference. [d] These assignements may be reversed.

p-toluenesulfonic acid monohydrate (50 mg). Triethylamine (3.5 mL) was added, and after 15 min the mixture was concentrated. A solution of the residue in 10:1 MeOH–water (55 mL) was refluxed for 8 h, at which time TLC (8:2 toluene–acetone) showed complete conversion of **30** to the major product **29**. The mixture was concentrated, toluene was added and evaporated, and the residue was chromatographed to give **29** in virtually theoretical yield; mp 172–173°C (from MeOH); $[\alpha]_D$ + 91° (*c* 0.9, $CHCl_3$); CIMS: *m/z* 284 $[(M + NH_4]^+)$, 267 $([M + H]^+)$. Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81. Found: C, 63.02; H, 6.86.

When the selective hydrolysis step was omitted, compound **30** was isolated by chromatography, using solvents containing 0.1% of Et_3N, as a crystalline mixture of α-methoxybenzyl isomers. CIMS: *m/z* 404 $([M + NH_4]^+)$, 387 $([M + H]^+)$; EIMS: *m/z* 386 $([M]^+)$, 355 $([M - OMe]^+)$. Definitive signals in the ^1H NMR spectrum were at δ: 5.71, 5.66, 5.63, 5.59 (4 s, PhCH, PhC*H*OCH_3), 4.84–4.82 (m, H-1), 3.76, 3.72 (2 bs, H-5), 3.57, 3.53, 3.52 and 3.42 (4 s, O*C*H_3, PhCHOC*H*$_3$); and in the ^{13}C NMR spectrum at δ: 102.92, 102.63, 101.00, 100.62 (Ph*C*H), 99.35, 99.00 (C-1), 73.54, 73.33 (C-4), 69.64, 69.58 (C-6), 68.56, 67.22 (C-2), 61.75, 61.65 (C-5), 55.28 (C-1-O*C*H_3), 53.95, 52.57 (PhCHO*C*H_3), 30.38 and 30.27 (C-3). Anal. Calcd for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 68.68; H, 6.91.

*Methyl 6-deoxy-3,4-*O*-isopropylidene-α-*D*-galactopyranoside* (**3**).—D-Fucose was converted[34] into its methyl α-pyranoside and the latter was treated[35,44] with 2,2-dimethoxypropane. After conventional workup, the mixture was chromatographed to give **3** in virtually theoretical yield as a syrup that solidified on standing. A portion was recrystallized from hexane–pentane; mp 38–39°C; $[\alpha]_D$ + 160° (*c* 1, $CHCl_3$); $[\alpha]_D$ + 171° (*c* 1, H_2O); [lit.[38] $[\alpha]_D$ – 160.0° (*c* 1.0, H_2O), lit.[40] $[\alpha]_D$ + 166.0° (*c* 1.7, H_2O)]. Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 55.15; H, 8.34.

*Methyl 3,4,6-tri-*O*-benzyl-3-*O*-p-methoxybenzyl-α-*D*-galactopyranoside* (**25**).—Benzyl bromide (6.15 mL, 51.7 mmol) was added dropwise to a stirred suspension of **18** (4.5 g, 14.3 mmol) and freshly powdered KOH (4.8 g, 85.5 mmol) in dimethyl sulfoxide (Me_2SO) (75 mL), and the mixture was stirred overnight at room temperature. Methanol (10 mL) was added, stirring was continued for 2 h, and the mixture was partitioned between CH_2Cl_2 and water. The organic layer was concentrated and coevaporated with toluene, and the residue was chromatographed (8:2 hexane–EtOAc) to give amorphous **25** (9.53 g, 97%); $[\alpha]_D$ + 50°

(*c* 1.2, $CHCl_3$); CIMS: *m/z* 602 ($[M + NH_4]^+$). Anal. Calcd for $C_{36}H_{40}O_7$: C, 73.95; H, 6.89. Found: C, 73.85; H, 6.94.

Methyl 2,4,6-tri-O-benzyl-α-D-galactopyranoside (**26**).—Oxidative deprotection of **25** (1.82 g, 3.1 mmol) with ceric ammonium nitrate (3.58 g, 6.5 mmol), as described for the preparation of **21** (*b*), followed by chromatography (9:1 toluene–EtOAc), gave amorphous **26** (1.61 g, 92%); $[\alpha]_D + 57°$ (*c* 1.2, $CHCl_3$); CIMS: *m/z* 482 ($[M + NH_4]^+$), 465 ($[M + H]^+$). Anal. Calcd for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94. Found: C, 72.34; H, 6.96.

Methyl 2,4,6-tri-O-benzyl-3-O-(imidazol-1-ylthiocarbonyl)-α-D-galactopyranoside (**27**).—A mixture of **26** (1.7 g, 3 mmol) and *N,N'*-thiocarbonyldiimidazole (1.07 g, 6 mmol) in dichloroethane (30 mL) was refluxed overnight. The solution was diluted with $CHCl_3$, washed successively with 5% HCl and water, dried, and chromatographed (9:1 hexane–acetone) to give amorphous **27** (1.92 g, 95%); $[\alpha]_D + 101°$ (*c* 1.1, $CHCl_3$) CIMS: *m/z* 575 ($[M + NH_4]^+$). Anal. Calcd for $C_{32}H_{34}N_2O_6S$: C, 66.88; H, 5.96; N, 4.87; S, 5.58. Found: C, 66.95; H, 6.00; N, 4.80; S, 5.56.

Methyl 2,4,6-tri-O-benzyl-3-deoxy-α-D-xylo-hexopyranoside (**28**).—A solution of **27** (1.92 g, 2.85 mmol) in toluene (50 mL) was treated overnight with tributyltin hydride (1.6 mL, 6 mmol) and 2,2'-azobis(2-methylpropionitrile) (83 mg, 0.5 mmol), as described for the preparation of **12**. More tributyltin hydride (500 μL, 1.9 mmol) and initiator (50 mg, 0.3 mmol) dissolved in toluene (10 mL) were added and, after an additional 6 h, TLC (8:2 hexane–acetone) showed that most of the starting material had been consumed and that one major product and a number of byproducts were formed. Concentration followed by chromatography (11:2 hexane–EtOAc) gave oily **28** (804 mg, 63%); $[\alpha]_D + 28°$ (*c* 1.1, $CHCl_3$); CIMS: *m/z* 466 ($[M + NH_4]^+$), 449 ($[M + H]^+$). Anal. Calcd for $C_{28}H_{32}O_5$: C, 74.98; H, 7.19. Found: C, 74.82; H, 7.22.

Further elution gave regenerated **26** (337 mg, 21%).

Methyl 2-O-benzoyl-3-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside (**33**).—Benzoyl chloride (5.9 mL, 50.8 mmol) was added, with stirring at 0°C, to a solution of **32** (ref 41, 15.6 g, 42 mmol) in pyridine (200 mL). The cooling bath was removed after 20 min and the mixture was kept at room temperature overnight. Methanol (10 mL) was added, and conventional workup gave **33** (19.6 g, 98%); mp 142–143°C (from MeOH); $[\alpha]_D + 135°$ (*c* 1.0, $CHCl_3$); CIMS: *m/z* 494 ($[M + NH_4]^+$), 477 ($[M + H]^+$). Anal. Calcd for $C_{28}H_{28}O_7$: C, 70.58; H, 5.92. Found: C, 70.47; H, 5.93.

Methyl 2-O-benzoyl-3,6-di-O-benzyl-4-O-(imidazol-1-ylthiocarbonyl)-α-D-glucopyranoside (**35**).—A suspension of **33** (4.76 g, 10 mmol), borane–Me_3N complex (4.38 g, 60 mmol) and powdered 4A molecular sieves (19 g) in THF (200 mL) was stirred at room temperature for 20 min. Aluminum chloride (8 g, 60 mmol) was added portionwise over 1 h and the mixture was stirred at 25°C for 6 h. The solids were filtered off and washed with toluene. The filtrates were combined and ice was added. Neutralization of the solution was performed via successive washings with 5% HCl, water, and aq $NaHCO_3$, and it was then dried and concentrated. The

residue was chromatographed (8:2 hexane–EtOAc) to give amorphous **34** (4.49 g, 94%); $[\alpha]_D + 99°$ (*c* 1.1, $CHCl_3$); CIMS: *m/z* 496 ($[M + NH_4]^+$). Anal. Calcd for $C_{28}H_{30}O_7$: C, 70.23; H, 6.31. Found: C, 70.06; H, 6.35.

A solution of **34** (914 mg, 1.91 mmol) and *N,N'*-thiocarbonyldiimidazole (749 mg, 4.2 mmol) in toluene (10 mL) was heated under reflux for 14 h, at which time the mixture contained only a trace of the starting material (TLC, 7:3 hexane–EtOAc). After concentration, a solution of the residue in EtOAc was washed successively with 5% HCl, water, and aq $NaHCO_3$, and it was then dried and concentrated. The residue was chromatographed (7:3 hexane–EtOAc) to afford **35** (984 mg, 86%); mp 106–107°C (from MeOH); $[\alpha]_D + 67°$ (*c* 1.0, $CHCl_3$); CIMS: *m/z* 589 ($[M + H]^+$). Anal. Calcd for $C_{32}H_{32}N_2O_7S$: C, 65.29; H, 5.48; N, 4.76; S, 5.45. Found: C, 65.36; H, 5.48; N, 4.75; S, 5.55.

*Methyl 2-O-benzoyl-3,6-di-O-benzyl-4-deoxy-α-*D-xylo-*hexopyranoside* (**36**).—A solution of **35** (965 mg, 1.64 mmol) in toluene (40 mL) was treated for 4 h with tributyltin hydride (910 μL, 3.4 mmol) and 2,2'-azobis(2-methylpropionitrile) (50 mg, 0.3 mmol), as described for the preparation of **13**. Chromatography (9:1 hexane–EtOAc) afforded first **36** (392 mg, 50%); $[\alpha]_D + 106°$ (*c* 1.1, $CHCl_3$); CIMS: *m/z* 496 ($[M + NH_4]^-$). Anal. Calcd for $C_{28}H_{30}O_6$: C, 72.71; H, 6.54. Found: C, 72.60; H, 6.55.

Eluted next was regenerated **34** (106 mg, 11%).

*Methyl 3,6-di-O-benzyl-4-deoxy-α-*D-xylo-*hexopyranoside* (**37**).—Compound **36** (250 mg, 0.52 mmol) was debenzoylated (Zemplén). After chromatography (11:9 hexane–EtOAc), the product **37** was obtained in virtually theoretical yield as a colorless oil; $[\alpha]_D + 106°$ (*c* 0.7, $CHCl_3$); CIMS: *m/z* 376 ($[M + NH_4]^+$), 359 ($[M + H]^+$). Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.15; H, 7.38.

*Methyl 2-O-benzyl-3,4-O-isopropylidene-6-O-(1-methoxy-1-methylethyl)-α-*D-*galactopyranoside* (**5**).—(±)-10-Camphorsulfonic acid (500 mg, 2.15 mmol) was added to a suspension of methyl α-D-galactopyranoside (9.7 g, 50 mmol) in 2,2-dimethoxypropane (350 mL), and the mixture was stirred at room temperature overnight. Triethylamine (25 mL) was added, and the solution was concentrated and immediately chromatographed on a column (3:1 → 2:1 hexane–EtOAc containing 0.1% Et_3N) to give **4** (10.54 g, 69%).

A solution of **4** (10.54 g, 34.4 mmol) in Me_2SO (175 mL) was treated with powdered KOH (3.86 g, 69 mmol) and benzyl bromide (4.9 mL, 41.2 mmol) as described for the preparation of **25**. Chromatography of the crude product (4:1 hexane–EtOAc containing 0.1% of Et_3N) afforded **5** as a colorless oil (13.2 g, 97%); CIMS: *m/z* 414 ($[M + NH_4]^+$). Anal. Calcd for $C_{21}H_{32}O_7$: C, 63.62; H, 8.13. Found: C, 63.67; H, 8.07.

*Methyl 2-O-benzyl-3,4-O-isopropylidene-*D-*galactopyranoside* (**6**).—A solution of crude **5** (from 24.7 mmol of **4**) in CH_2Cl_2 (300 mL) was shaken with ice-cold 5% CF_3CO_2H (20 mL) until TLC (13:7 hexane–EtOAc) showed complete conversion of **5** into a more polar product. The organic phase was washed with 5% $NaHCO_3$, dried, and concentrated, and the residue was chromatographed to give **6** in

virtually theoretical yield; mp 108–109°C (from EtOH); $[\alpha]_D$ + 98° (*c* 1.0, $CHCl_3$); CIMS: *m/z* 342 ($[M + NH_4]^+$). Anal. Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 746. Found: C, 63.00; H, 7.44.

Methyl 6-O-benzoyl-2-O-benzyl-3,4-O-isopropylidene-α-D-galactopyranoside (**8**).—Crystalline **6** (5.76 g, 17.8 mmol) was benzoylated conventionally, and the fully protected **8** was isolated by chromatography (9 : 1 hexane–acetone) in virtually theoretical yield; $[\alpha]_D$ + 88° (*c* 0.9, $CHCl_3$); CIMS: *m/z* 446 ($[M + NH_4]^+$), 429 ($[M + H]^+$). Anal. Calcd for $C_{24}H_{28}O_7$: C, 67.27; H, 6.57. Found: C, 67.22; H, 6.59.

Methyl 6-O-benzoyl-2-O-benzyl-α-D-galactopyranoside (**9**).—To a solution of crude **8** (from 12.3 g, 38 mmol of **6**) in acetic acid (100 mL) was added water (10 mL), and the mixture was stirred at 80°C until TLC (7 : 3 hexane–acetone) showed that the conversion **8** → **9** was complete. After concentration, the residue was chromatographed, to yield **9** (13.0 g, 88%) as a glassy solid; $[\alpha]_D$ + 91° (*c* 1.0, $CHCl_3$); CIMS: *m/z* 406 ($[M + NH_4]^+$), 389 ($[M + H]^+$). Anal. Calcd for $C_{21}H_{24}O_7$: C, 64.94; H, 6.23. Found: C, 64.96; H, 6.28.

Methyl 2-O-benzyl-α-D-galactopyranoside (**7**).—A solution of **6** (7.94 g, 20 mmol) in acetic acid (80%, 50 mL) was kept at 70°C for 1.5 h, at which time TLC showed that the reaction was practically complete. After concentration, and the additions evaporation of toluene, product **7** was sufficiently pure for the next step. A portion crystallized from EtOAc had mp 124–125°C; $[\alpha]_D$ + 110° (*c* 0.9, $CHCl_3$); CIMS: *m/z* 302 ($[M + NH_4]^+$). Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.07. Found: C, 59.06; H, 7.14.

Methyl 3,6-di-O-benzoyl-2-O-benzyl-α-D-galactopyranoside (**14**).—Benzoyl chloride (4.63 mL, 39.9 mmol) was added, dropwise and with stirring at −30°C, to a solution of **7** (5.34 g, 19 mmol) in pyridine (190 mL). The mixture was allowed to warm to room temperature and stirred overnight. Methanol was added to destroy the excess of the reagent, and after conventional workup the crude material was chromatographed (8 : 2 hexane–EtOAc) to yield **14** (6.9 g, 74%); mp 98.5–99.5°C (from EtOAc–hexane); $[\alpha]_D$ + 61° (*c* 0.9, $CHCl_3$); CIMS: *m/z* 510 ($[M + NH_4]^+$), 493 ($[M + H]^+$). Anal. Calcd for $C_{28}H_{28}O_8$: C, 68.28; H, 5.73. Found: C, 68.10; H, 5.79.

Methyl 3,6-di-O-benzoyl-2-O-benzyl-4-O-(imidazol-1-ylthiocarbonyl)-α-D-galactopyranoside (**15**).—Compound **14** (2.4 g, 5 mmol) was treated with *N,N'*-thiocarbonyldiimidazole (1.78 g, 10 mmol) as described for the preparation of **11**. Chromatography of the crude material (7 : 3 hexane–EtOAc) gave **15** (2.9 g, 96%) as a white foam; $[\alpha]_D$ + 89° (*c* 1.2, $CHCl_3$); CIMS: *m/z* 603 ($[M + H]^+$). Anal. Calcd for $C_{32}H_{30}N_2O_8S$: C, 63.78; H, 5.02; N, 4.65; S, 5.32. Found: C, 63.92; H, 5.12; N, 4.52; S, 5.24.

Methyl 3,6-di-O-benzoyl-2-O-benzyl-4-deoxy-α-D-xylo-hexopyranoside (**16**).—Compound **15** (2.53 g, 4.4 mmol) was treated with tributyltin hydride (2.6 mL, 9.8 mmol) and 2,2'-azobis(2-methylpropionitrile) (161 mg, 0.98 mmol) in toluene (150 mL) as described for the preparation of **12**. Chromatography (9 : 1 → 8 : 2 hexane–EtOAc) gave **16** in virtually theoretical yield; mp 91.5–92.5°C (from MeOH);

$[\alpha]_D$ + 80° (*c* 1.0, $CHCl_3$); CIMS: *m/z* 494 ($[M + NH_4]^+$), 477 ($[M + H]^+$). Anal. Calcd for $C_{28}H_{28}O_7$: C, 70.57; H, 5.92. Found: C, 70.58; H, 5.94.

*Methyl 3,6-di-O-benzoyl-4-deoxy-α-*D*-xylo-hexopyranoside* (**17**).—A mixture of **16** (2 g, 4.2 mmol) and 10% Pd–C (300 mg) in 1:5 acetone–EtOH (50 mL) was stirred overnight under H_2. Additional catalyst (200 mg) was added, and hydrogenation was continued for 24 h. Conventional workup afforded **17** (96%); mp 142–143°C (from MeOH); $[\alpha]_D$ + 109° (*c* 0.9, $CHCl_3$); CIMS: *m/z* 404 ($[M + NH_4]^+$), 387 ($[M + H]^+$). Anal. Calcd for $C_{21}H_{22}O_7$: C, 65.28; H, 5.74. Found: C, 65.20; H, 5.74.

*Methyl O-(2,3,4-tri-O-benzoyl-α-*L*-rhamnopyranosyl-(1 → 2)-6-deoxy-3,4-O-isopropylidene-α-*D*-galactopyranoside* (**40**).—A solution of **3** (1.30 g, 6 mmol), **39** (4.5 g, 8.34 mmol), and *sym*-collidine (996 μL, 7.56 mmol) in CH_2Cl_2 (30 mL) was added with stirring at −20°C to a suspension of AgOTf (2.46 g, 9.6 mmol) in CH_2Cl_2 (10 mL). After 2 min, the cooling bath was removed, and when the mixture became acidic to litmus (~ 7 min), *sym*-collidine (150 μL) was added to neutralize the acid formed. TLC (3:1 hexane–EtOAc) showed complete disappearance of **3** and the formation of one major product. The mixture was filtered through Celite, the filtrate was washed with a mixture of aq 5% $NaHCO_3$ and 5% $Na_2S_2O_3$, then water, dried, and concentrated. Evaporation of water from the residue removed the excess of *sym*-collidine. Chromatography (11:2 hexane–acetone) gave amorphous **40** (3.93 g, 97%), $[\alpha]_D$ + 168° (*c* 1.0, $CHCl_3$); CIMS: *m/z* 694 ($[M + NH_4]^+$). Anal. Calcd for $C_{37}H_{40}O_{12}$: C, 65.67; H, 5.96. Found: C, 65.78; H, 6.03.

*Methyl O-(2,3,4-tri-O-benzoyl-α-*L*-rhamnopyranosyl)-(1 → 2)-6-deoxy-α-*D*-galactopyranoside* (**41**).—Water (1.8 mL) was added at 80°C to a solution of **40** (4.07 g, 6.03 mmol) in acetic acid (18 mL) and the mixture was stirred at that temperature for 6 h. After concentration and coevaporation of residual acetic acid with toluene, chromatography (3:1 hexane–EtOAc) afforded **41** (3.76 g, 98%); $[\alpha]_D$ + 174° (*c* 1.0, $CHCl_3$); CIMS: *m/z* 654 ($[M + NH_4]^+$). Anal. Calcd for $C_{34}H_{36}O_{12}$: C, 64.14; H, 5.70. Found: C, 64.35; H, 5.93.

*Methyl O-α-*L*-rhamnopyranosyl-(1 → 2)-6-deoxy-3,4-O-isopropylidene-α-*D*-galactopyranoside* (**42**).—Debenzoylation (Zemplén) of **40** (300 mg, 0.44 mmol) afforded **42** as the sole product, as seen by TLC (20:1 $CHCl_3$–MeOH) of the mixture before workup. Partial loss of the isopropylidene group occurred during workup, but chromatography (9:1 $CHCl_3$–MeOH) afforded **42** (99 mg, 62%); $[\alpha]_D$ + 62° (*c* 0.3, $CHCl_3$); CIMS: *m/z* 382 ($[M + NH_4]^+$). Anal. Calcd for $C_{16}H_{28}O_9$: C, 52.74; H, 7.75. Found: C, 52.66; H, 7.71.

Further elution gave the fully deprotected **43** (38 mg, 17%).

*Methyl O-α-*L*-rhamnopyranosyl-(1 → 2)-6-deoxy-α-*D*-galactopyranoside* (**43**).—Conventional debenzoylation (Zemplén) of **41** (2.24 g, 3.5 mmol) gave **43** (987 mg, 87%); mp 191–192°C (from MeOH–EtOAc); $[\alpha]_D$ + 58° (*c* 0.6, MeOH); CIMS: *m/z* 342 ($[M + NH_4]^+$). Anal. Calcd for $C_{13}H_{24}O_9 \cdot 0.5H_2O$: C, 46.84; H, 7.55. Found: C, 46.92; H, 7.58.

*Methyl O-(2,3,4-tri-O-benzoyl-α-*L*-rhamnopyranosyl)-(1 → 2)-4,6-O-benzylidene-3-deoxy-α-*D*-xylo-hexopyranoside* (**44**).—A solution of **29** (1.34 g, 5 mmol), **39** (3.77

g, 7 mmol), and 2,4,6-trimethylpyridine (830 μL, 6.3 mmol) in CH_2Cl_2 (25 mL) was treated with AgOTf (2.05 g, 8 mmol) as described for the preparation of **40**. TLC (72:28 hexane–EtOAc) showed the absence of the starting **29** and the formation of one major product. After conventional workup, chromatography (3:1 hexane–EtOAc) gave amorphous **44** (3.36 g, 93%); $[\alpha]_D$ + 140° (*c* 1.0, $CHCl_3$); CIMS: *m/z* 742 ($[M + NH_4]^+$). Anal. Calcd for $C_{40}H_{44}O_{12}$: C, 67.95; H, 5.56. Found: C, 68.06; H, 5.60.

Methyl O-*(2,3,4-tri-*O*-benzoyl-α-*L*-rhamnopyranosyl)-(1 → 2)-3-deoxy-α-*D*-xylo-hexopyranoside* (**45**).—Compound **44** (1.08 g, 1.5 mmol) was hydrogenolyzed as described for the preparation of **43**. After processing, the crude product in solvent was passed through a small column of silica gel to remove residual catalyst, and concentrated to afford **45** (895 mg, 94%); $[\alpha]_D$ + 154° (*c* 1.0, $CHCl_3$); CIMS: *m/z* 654 ($[M + NH_4]^+$). Anal. Calcd for $C_{34}H_{36}O_{12}$: C, 64.14; H, 5.70. Found: C, 63.95; H, 5.85.

Methyl O-*α*-L-*rhamnopyranosyl-(1 → 2)-4,6-*O*-benzylidene-3-deoxy-α-*D*-xylo-hexopyranoside* (**46**).—Debenzoylation (Zemplén) of **44** (724 mg, 1 mmol) afforded, after chromatography, amorphous **46** (354 mg, 86%); $[\alpha]_D$ + 13° (*c* 0.5, acetone); mp 167.5–168.5°C (from MeOH); CIMS: *m/z* 430 ($[M + NH_4]^+$). Anal. Calcd for $C_{20}H_{28}O_9 \cdot 0.5H_2O$: C, 57.00; H, 6.93. Found: C, 57.03; H, 7.06.

Methyl O-*α*-L-*rhamnopyranosyl-(1 → 2)-3-deoxy-α*-D-xylo-*hexopyranoside* (**47**).—Debenzoylation (Zemplén) of **45** (500 mg, 0.78 mmol) gave **47** (281 mg, 88%), mp 207–208°C (from MeOH); $[\alpha]_D$ + 21.2° (*c* 0.3, MeOH); CIMS: *m/z* 342 ($[M + NH_4]^+$). Anal. Calcd for $C_{13}H_{24}O_9$: C, 48.14; H, 7.46. Found: C, 48.07; H, 7.49.

Methyl O-*(2,3,4-tri-*O*-benzoyl-α-*L*-rhamnopyranosyl)-(1 → 2)-3,6-di-*O*-benzoyl-4-deoxy-α-*D*-xylo-hexopyranoside* (**48**).—A mixture of **17** (756 mg, 1.95 mmol), **39** (1.48 g, 2.74 mmol), and *sym*-collidine (325 μL, 2.46 mmol) in CH_2Cl_2 (10 mL) was treated with AgOTf as described for the preparation of **40**. TLC (7:3 hexane–EtOAc) showed that the starting **17** was consumed, and that one major product was formed. Chromatography (4:1 → 8:3 hexane–EtOAc) gave amorphous **48** (1.51 g, 92%); $[\alpha]_D$ + 146° (*c* 1.0, $CHCl_3$); CIMS: *m/z* 862 ($[M + NH_4]^+$). Anal. Calcd for $C_{48}H_{44}O_{14}$: C, 68.24; H, 5.25. Found: C, 68.30; H, 5.32.

Methyl O-*α*-L-*rhamnopyranosyl-(1 → 2)-4-deoxy-α*-D-xylo-*hexopyranoside* (**49**).—Compound **48** (833 mg, 0.98 mmol) was debenzoylated (Zemplén) as described above, to afford **49** (267 mg, 84%) as a white amorphous solid. The material, which appeared pure (TLC, NMR), retained solvents and/or moisture tenaciously, and correct analytical data could not be obtained; $[\alpha]_D$ +44° (*c* 0.8, MeOH); CIMS: *m/z* 342 ($[M + NH_4]^+$).

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