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Preliminary communication

Application of ferric chloride-catalyzed glycosylation to a synthesis of glycolipids

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Endotoxic lipopolysaccharide is a prominent, macromolecular component of the outer membrane of Gram-negative bacteria, and most of its biological activities have been shown to be dependent upon structures in the lipid A component[1,2]. In this connection, it has been reported that some simple, synthetic glycoplipids, such as *N*-fatty acylated 2-amino-2-deoxy-D-glucose derivatives, exhibit potent, immunostimulatory activities[3–5].

In view of this fact, we sought a facile preparation of *N*-fatty acylated 2-amino-2-deoxy-β-D-glucopyranosides, which seem to be key intermediates for the synthesis of a variety of complex glycolipids. As outlined in previous papers[6,7], we recently developed a new, convenient, and apparently general, procedure for the synthesis of β-glycosides of 2-(acylamino)-2-deoxyglycopyranoses. This "direct" glycosylation, catalyzed by ferric chloride, appeared suitable for our purpose. The present communication describes an application of this method to glycolipid synthesis.

1,3,4,6-Tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranose[8] (**1**) was treated with do-, tetra-, hexa-, and octa-decanoyl (lauroyl, myristoyl, palmitoyl, and stearoyl) chlorides in 2:1 (v/v) chloroform–pyridine solution, to give the crystalline 1,3,4,6-tetra-*O*-acetyl-2-(acylamino)-2-deoxy-β-D-glucopyranoses **2**–**5** in almost quantitative yields. All compounds of this series were recrystallized from ethanol (see Table I). The 3-oxomyristoyl derivative **12** {amorphous, $[\alpha]_D^{20}$ +11.3° (*c* 0.9, chloroform)} was synthesized by treatment of **1** with *N*-(3-oxomyristoyloxy)succinimide, which is readily prepared by stirring 3-oxomyristic acid[9,10] with dicyclohexylcarbodiimide and *N*-hydroxysuccinimide in dry oxolane.

The ferric chloride-catalyzed glycosylation was conducted by treatment of compounds **2**–**5** and **12** (1 mol. equiv.) with benzyl or allyl alcohol (5 mol. equiv.) in the presence of anhydrous ferric chloride (1.5 mol. equiv.) in dichloromethane as reported earlier[6] to give the corresponding β-glycosides **6**–**11** (see Table I) and **13** {amorphous, $[\alpha]_D^{20}$ –23.6° (*c* 1, chloroform)} in high yields (75–90%). Compound **12** was completely converted into **13** within 3 h, whereas **2**–**5** required reaction overnight. We found that, when the treatment of **3** with ferric chloride was conducted without alcohol (an excellent procedure for oxazoline synthesis described by Matta and Bahl[11], and very recently by Handa *et al.*[12]),

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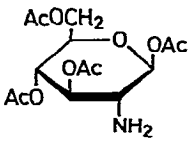

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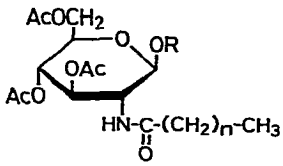
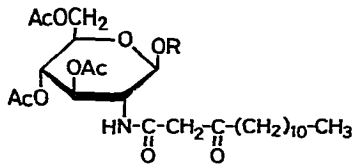
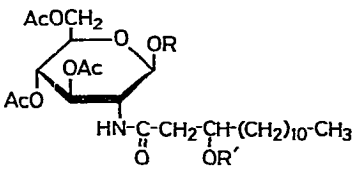


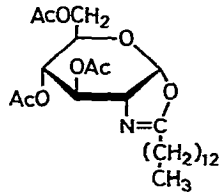
2–5 R = Ac
6–9 R = Bn
10,11 R = All



12 R = Ac
13 R = Bn



14 R = Ac, R′ = H
15 R = Ac, R′ = Ac
16 R = Bn, R′ = H
17 R = Bn, R′ = Ac



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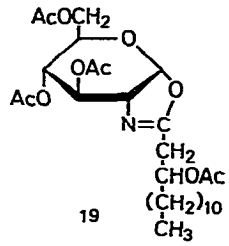

19

Bn = benzyl All = allyl

TABLE I

PHYSICAL PROPERTIES OF 1,3,4,6-TETRA-*O*-ACETYL-2-(ACYLAMINO)-2-DEOXY-β-D-GLUCOPYRANOSES (2–5) AND ALKYL 3,4,6-TRI-*O*-ACETYL-2-(ACYLAMINO)-2-DEOXY-β-D-GLUCOPYRANOSIDES (6–11)

Value of n	*Compd. no.*	*R = Ac*		*Compd. no.*	*R = Bn*		*Compd. no.*	*R = All*	
		M.p. (°C)	$[\alpha]_D^{20}$ *(degrees)* [a]		*M.p. (°C)*	$[\alpha]_D^{20}$ *(degrees)* [a]		*M.p. (°C)*	$[\alpha]_D^{20}$ *(degrees)* [a]
10	2	134–135	+5.0	6	128–129	–28			
12	3	136–137	+3.5	7	124–125	–27	10	118–120	–5.5
14	4	136–138	+3.6	8	123–124	–27	11	117–120	–5.2
16	5	138–140	+3.3	9	126–127	–26			

[a] Specific rotations determined in chloroform, *c* 1.

the new oxazoline **18** was obtained in almost quantitative yield; the compound, purified by rapid chromatography on a column of silica gel with chloroform as the solvent, was a syrup, $[\alpha]_D^{20}$ +13.3° (*c* 1, chloroform). The formation of oxazoline intermediates in the course of the reaction with alcohols was observed for all of the β-acetates **2–5**, whereas compound **12** did not give such a stable oxazoline. This difference might be related to the lower reactivity of the former β-1-acetates in the glycosylation just described.

Treatment of **12** with sodium borohydride in methanol solution gave **14** as an amorphous solid, $[\alpha]_D^{20}$ +6.7° (*c* 1, chloroform), a part of which was acetylated to yield **15**

{amorphous, $[\alpha]_D^{20}$ +2.9° (*c* 0.5, chloroform)}. Similarly, the benzyl glycoside **13** was reduced to **16** {amorphous, $[\alpha]_D^{20}$ −25.8° (*c* 0.6, chloroform)}. Compound **15** was treated with ferric chloride, with and without benzyl alcohol, as already described, to afford **17** as an amorphous solid, $[\alpha]_D^{20}$ −22° (*c* 0.5, chloroform), and the corresponding oxazoline **19** as a syrup, $[\alpha]_D^{20}$ +21.6° (*c* 0.5, chloroform), in almost quantitative yields.

The new oxazolines **18** and **19**, which may be intermediates in the direct conversion of β-1-acetates into β-glycosides as described here, may prove useful for the synthesis of some analogs of lipid A containing a variety of acylamido residues.

All new compounds were characterized by i.r. and n.m.r. spectra, and had elemental compositions in satisfactory accord with theory.

ACKNOWLEDGMENTS

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REFERENCES

1 C. Galanos, O. Lüderitz, E. T. Rietschel, and O. Westphal, *Int. Rev. Biochem.*, 14 (1977) 239–335.
2 O. Lüderitz, C. Galanos, V. Lehmann, H. Mayer, E. T. Rietschel, and J. Weckesser, *Naturwissenschaften*, 65 (1978) 578–585.
3 D. L. Rosenstreich, J. Asselineau, S. E. Mergenhagen, and A. Nowotny, *J. Exp. Med.*, 140 (1974) 1404–1409.
4 U. H. Behling, B. Campbell, C.-M. Chang, C. Rumpf, and A. Nowotny, *J. Immunol.*, 117 (1976) 847–851.
5 R. C. Butler and A. Nowotny, *Cancer Immunol. Immunother.*, 6 (1979) 255–262.
6 M. Kiso and L. Anderson, *Carbohydr. Res.*, 72 (1979) C12–C14.
7 M. Kiso and L. Anderson, *Carbohydr. Res.*, 72 (1979) C15–C17.
8 M. Bergmann and L. Zervas, *Ber.*, 64 (1931) 975–980.
9 M. A. Mitz, A. E. Axelrod, and K. Hofmann, *J. Am. Chem. Soc.*, 72 (1950) 1231–1232.
10 W. Wierenga and H. I. Skulvick, *J. Org. Chem.*, 44 (1979) 310–311.
11 K. L. Matta and O. P. Bahl, *Carbohydr. Res.*, 21 (1972) 460–464.
12 V. K. Handa, J. J. Barlow, and K. L. Matta, *Carbohydr. Res.*, 76 (1979) C10–C12.