Tetrahedron Letters, Vol.32, No.43, pp 6175-6178, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

An approach towards the synthesis of 1,2-*trans* glycosyl phosphates *via* iodonium ion assisted activation of thioglycosides

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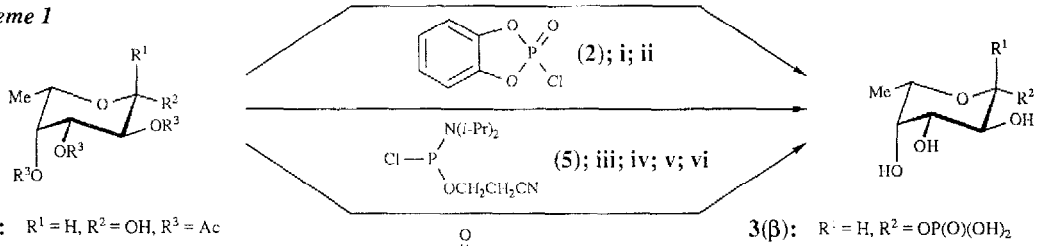
Abstract: Phosphorylation of benzoylated ethyl 1,2-*trans* 1-thioglycosides with dibenzyl phosphate in the presence of NIS gave, after removal of all protecting groups, 1,2-*trans* glycosyl phosphates. The scope of the stereoselective method was demonstrated by the synthesis of GDP-fucose and the disaccharide α-D-Glc*p*-(1→3)-α-L-Rha*p*-1-PO_4^-.

It is well established now that 1,2-*cis* or *trans* glycosyl phosphates are characteristic structural elements of many biologically important molecules. For example, guanosine 5'-(β-L-fucopyranosyl)-diphosphate (GDP-fucose) acts as donor substrate for the enzyme Lewis α(1→4) fucopyranosyltransferase. In addition, the repeating sugar units of several antigenic teichoic acids are linked by the same type of phosphodiester bonds. Thus far, two main routes suitable for the stereoselective introduction of anomeric phosphate functions have been described.

Scheme 1



1(β): R^1 = H, R^2 = OH, R^3 = Ac
4(α): R^1 = OH, R^2 = H, R^3 = Bn
7(α): R^1 = OC(NH)CCl_3, R^2 = H, R^3 = Ac

3(β): R^1 = H, R^2 = OP(O)$(OH)_2$
6(α): R^1 = OP(O)$(OH)_2$, R^2 = H

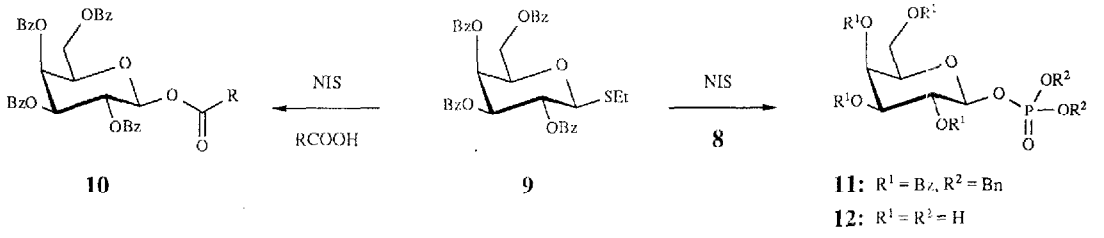
Reagents: (i) Br_2/H_2O; (ii) $Ba(OH)_2$; (iii) 1-H-tetrazole/$HOCH_2CH_2CN$; (iv) t-BuOOH; (v) NaOH; (vi) H_2/Pd(C); (vii) Et_3N/MeOH/H_2O.

The first one, originally proposed by Behrman *et al.*[1], is exemplified by the synthesis (Scheme 1) of the 1,2-*trans* L-fucopyranosyl phosphate (3β) *via* direct phosphorylation with retention of configuration of the anomeric hydroxyl in the L-fucopyranose derivative **1** with the monofunctional phosphorylating agent **2**. Later on, it was reported[2] that the efficacy of the phosphorylation could be increased substantially by using the phosphitylating agent **5**. For instance, phosphitylation of **4** with **5**, and further processing, gave the corresponding 1,2-*cis* L-fucopyranosyl phosphate (6α). The second approach, which comprises a S_N2-like

substitution of a suitable leaving group at the anomeric centre by a phosphonic acid derivative, was recently reported by Schmidt *et al.*[3]. For example, replacement of the trichloroacetimidate function in **7α** with dibenzyl phosphate (**8**) gave, after further elaboration, the 1,2-*trans* L-fucopyranosyl phosphate (**3β**) in a good yield.

We report here that benzoylated 1,2-*trans* ethyl 1-thioglycopyranosides (*e.g.* **9**, **14** and **20**) are convenient starting compounds for the synthesis of 1,2-*trans* glycosyl phosphates (*e.g.* **12**, 3 and **22**). Earlier studies from our laboratory[4] (Scheme 2) showed *inter alia* that *N*-iodosuccinimide (NIS) mediated activation

Scheme 2

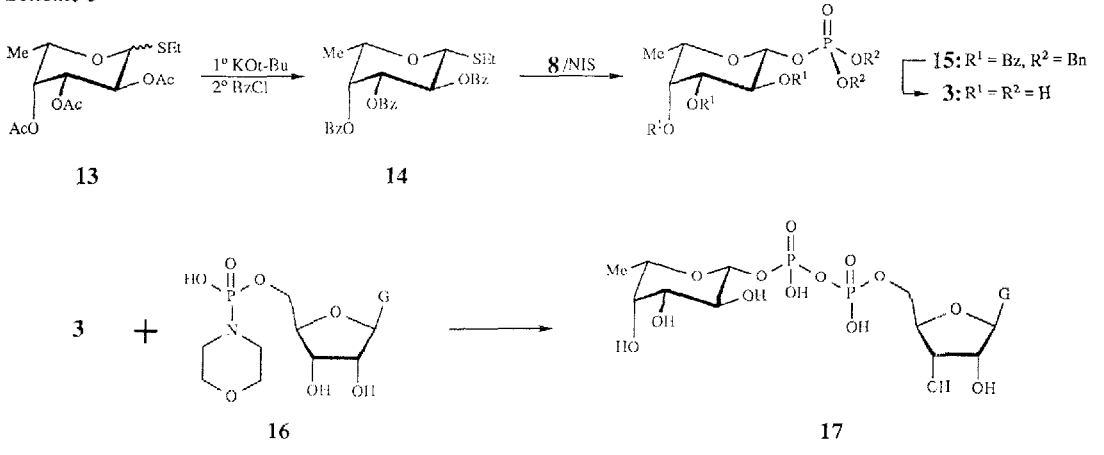


10 **9** **11:** $R^1 = Bz, R^2 = Bn$; **12:** $R^1 = R^2 = H$

of ethyl 2,3,4,6-tetra-*O*-benzoyl 1-thio-β-D-galactopyranoside (**9**) in the presence of Brønsted acids resulted in the formation of the corresponding 1,2-*trans* glycosidic esters **10**. On the basis of this finding, it was to be expected that replacement of RCOOH by phosphoric acid derivatives would give access to 1,2-*trans*-glycosyl phosphates. Indeed, treatment of **9** (1 mmol) with **8** (1 mmol) in the presence of NIS (1.2 mmol) for 20 min at 20°C, afforded, after work-up and purification by flash chromatography, the homogeneous 1,2-*trans* phosphotriester derivative **11** (δ_p -2.39 ppm) in 80% yield. Catalytic hydrogenolysis (H_2/Pd/C) of the benzyl groups and subsequent debenzoylation with sodium hydroxide followed by neutralization (Dowex 50WX4, H^+-form) gave **12** (δ_p 0.88 ppm) in 75% yield. The ^{1}H-NMR data[5] of **12** clearly indicated that the two-stage deblocking process proceeded with retention of anomeric configuration.

The successful outcome of the phosphorylation procedure, urged us to find out whether this stereoselective approach could be adopted for the synthesis of valuable 1,2-*trans* glycosyl phosphate derivatives. The first example, which entails the synthesis of GDP-fucose (*i.e.* **17**), is outlined in Scheme

Scheme 3



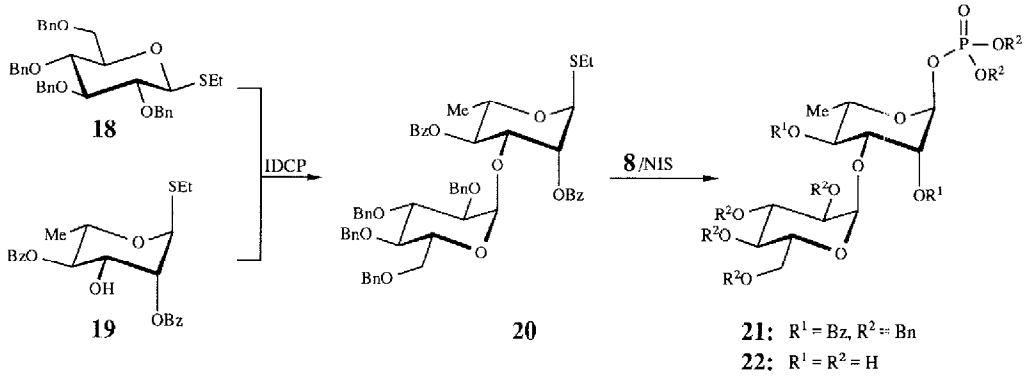
13 **14**

16 **17**

3, and commences[6] with the preparation of ethyl 2,3,4-tri-*O*-benzoyl-1-thio-β-L-fucopyranoside (**14**). To this end, an anomeric mixture of easily accessible **13**[7] was deacetylated (KOtBu/MeOH) followed by benzoylation (BzCl/pyridine) to give, after separation of the individual anomers by silica gel chromatography, homogeneous **14** in 55% overall yield. NIS mediated phosphorylation of **14** in the presence of **8** furnished, after flash chromatography, anomerically pure **15** (δ_p -2.25 ppm) as evidenced by NMR-spectroscopy. Two-stage deblocking of **15**, under the conditions used for the conversion of **11**→**12**, gave β-L-fucopyranosyl phosphate[5] (**3**; δ_p 1.87 ppm) in 60% overall yield. Introduction of the pyrophosphate function in GDP-fucose (**17**) could be realized by a slight, but essential, modification of the procedure recently published by Schmidt *et al.*.[3] Thus, the bis(tri-*n*-octylammonium salt) of **3** (1 mmol) was coupled with commercially available guanosine 5'-phosphoromorpholidate (**16**; *N,N'*-dicyclohexyl-4-morpholine carboxamidinium salt; 1 mmol) in dry DMF (50 mL). Work-up, after 14 h at 50°C, and purification[8] gave **17** (Na^+-salt : 42% yield), the ^{1}H-, ^{13}C- and ^{31}P-NMR data of which were in excellent accord with those reported.[1a,3,9] In this respect, it is of interest to note that the condensation of **3** with **16** in the solvent DMF and at elevated temperature resulted not only in a reproducible yield of **17**, but also in a considerable decrease in reaction time.[10]

The scope of the new phosphorylation procedure was further demonstrated (Scheme 4) by the successful synthesis of 3-*O*-(α-D-glucopyranosyl)-α-L-rhamnopyranosyl phosphate (**22**), which is a fragment of the repeating unit from the linear capsular polysaccharide [→4-β-D-Man*p*NAc-(1→4)-α-D-Glc*p*-(1→3)-α-L-Rha*p*-(1-PO_4^-)→] of *Streptococcus pneumoniae* type 19A.[11] The α(1→4) linkage in dimer **20** was introduced (Scheme 4) by the chemoselective condensation[12] of the armed and disarmed thioglycosides **18** and **19**,[13] respectively. Thus iodonium dicollidine perchlorate (IDCP; 2 mmol) mediated glycosylation (90 min at 20°C)

Scheme 4



of acceptor **19** (1 mmol) with donor **18** (1 mmol) gave, after purification by silica gel column chromatography, dimer **20** in 80% yield. Subsequent phosphorylation (1 h at 20°C) of **20** (0.24 mmol) in the presence of equal amounts (0.36 mmol) of NIS and **8** furnished, after purification by flash chromatography, the 1,2-*trans* glycosyl phosphotriester **21** (δ_p -2,36 ppm) in 83% yield. Two-step deblocking (see conversion **11**→**12**) afforded homogeneous **22** (80% yield, δ_p -1.36 ppm), the ^{1}H- and ^{13}C-NMR data[5] of which were in excellent agreement with the proposed structure.

In conclusion, the stereoselective phosphorylation procedure described in this paper promises to be a valuable tool for the preparation of biologically important 1,2-*trans* glycosyl phosphates.

Acknowledgement

We wish to thank GlycoGen, Inc. (San Francisco) for financial support.

References and Notes

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3. Schmidt, R.R. Wegmann, B.; Jung, K.-H. *Liebigs Ann. Chem.* **1991**, 121.
4. Veeneman, G.H; van Leeuwen, S.H.; van Boom, J.H. *Tetrahedron Lett.* **1990**, *31*, 1331.
5. All new compounds were fully characterized by spectroscopic techniques (^{1}H-, ^{13}C- and ^{31}P-NMR) and their molecular formulas were established by high resolution mass spectroscopy. Relevant ^{1}H-, ^{13}C- and ^{31}P-NMR data of compounds **3**, **12**, **17** and **22** were as follows. ^{1}H-NMR data (δ-values): **3**; 4.74 (dd, 1H, H-1, $J_{1,2} = J_{H,P} \approx 7.6$ Hz), 3.60 (dd, 1H, H-3, $J_{3,4} = 3.3$ Hz), 3.40 (dd, 1H, H-2, $J_{2,3} = 9.8$ Hz). **12**; 4.81 (dd, 1H, H-1, $J_{1,2} = 7.5$ Hz), 3.66 (dd, 1H, H-3, $J_{3,4} = 3.3$ Hz), 3.51 (dd, 1H, H-2, $J_{2,3} = 10.0$ Hz). **17**; 8.10 (s, 1H, H-8), 5.90 (d, 1H, H-1', $J_{1',2'} = 5.9$ Hz), 1.24 (d, 3H, H-6", $J_{6",5"} = 6.4$ Hz). **22**; 5.30 (dd, 1H, H-1, $J_{1,2} = 1.6$ Hz, $J_{H,P} = 7.8$ Hz), 5.02 (d, 1H, H-1', $J_{1',2'} = 3.6$ Hz). ^{13}C-NMR: **3**; 98.1 (d, C-1, $^2J_{C,P} = 4.4$ Hz ($J_{C,H} = 161$ Hz)). **12**; 98.3 (d, C-1, $^2J_{C,P} = 4.4$ Hz). **17**; (C-6"), 87.7 (C-1'), 99.3 (C-1", $^2J_{C,P} = 5.0$ Hz). **22**; 96.2 (C-1'), 95.7 (d, C-1, $^2J_{C,P} = 4.4$ Hz), 68.0 (d, C-2, $^3J_{C,P} = 7.3$ Hz). ^{31}P-NMR (D_2O): **17**; -12.5 (d, 1P, J = 19.3 Hz) and -10.8 (d, 1P, J 19.3 Hz).
6. Recently, Hindsgaul *et al.* (see ref. 9) used 2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl bromide as the starting compound. However, reaction of the bromide with dibenzyl phosphate (**8**) gave, after removal of the protecting groups, L-fucopyranosyl phosphate (**3**) as a mixture of anomers (β : α = 15 :1)
7. Prepared by treating 1,2,3,4-tetra-*O*-acetyl-α-L-fucopyranose (see ref. 1) with $SnCl_4$ in the presence of EtSH (see: G.H. Veeneman *et al.*, *J. Carbohydr. Chem.* **1990**, *9*, 783).
8. Crude **17** was purified (eluent: 0.15 M triethylammonium bicarbonate; flow-rate: 2 mL/min) on a HiLoad Sephacryl S-100 HR26/160 (Pharmacia) column. Pure **17** (R_t 313 min) thus obtained was converted into the sodium-salt (Dowex 50WX4, Na^+-salt).
9. Gokhale, U.B.; Hindsgaul, O.; Palcic, M.M. *Can.J. Chem.*, **1990**, *68*, 1063.
10. In comparison, condensation of **3** with **16** in pyridine (see ref. 1a and 9) or pyridine-DMF (see ref. 3) for 4-5 days at 20°C gave GDP-fucose in variable yields [*i.e.* 50% (1a); 27% (9); 22% (3)].
11. Katzenellenbogen, E.; Jennings, H.J. *Carbohydrate Res.*, **1983**, *124*, 235.
12. Veeneman, G.H.; van Boom, J.H. *Tetrahedron Lett.* **1990**, *31*, 275.
13. Regioselective tritylation of ethyl 1-thio-α-L-rhamnopyranoside (see: G.H. Veeneman *et al.*, *Tetrahedron* **1989**, *45*, 7433) with *p*-anisylchlorodiphenylmethane gave 3-*O*-(*p*-methoxytrityl)-1-thio-α-L-rhamnopyranoside in 70% yield. Benzoylation (BzCl/pyridine) followed by acidic hydrolysis (80% HOAc) furnished **19** in 80% yield.

(Received in UK 8 July 1991)