Design, Development and Utility of Glycosyl Donors Bearing an Acetoxymethoxy Leaving Group

Hari Babu Mereyala* and Srinivas Reddy Gurrala
Organic Division-III, Indian Institute of Chemical Technology, Hyderabad 500007, India

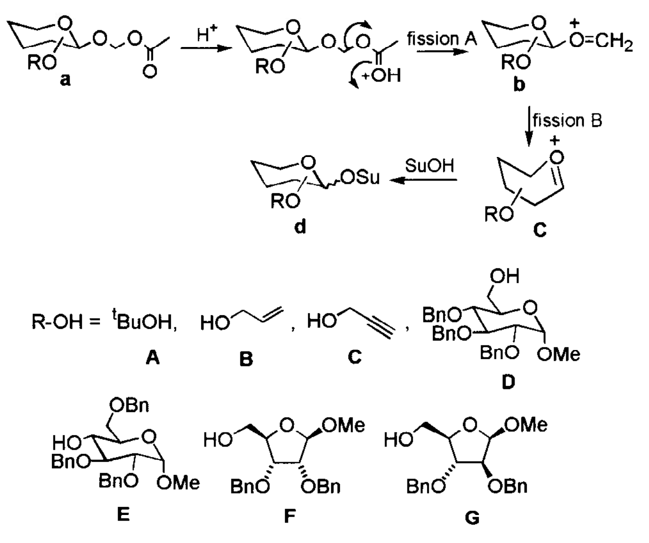
(Received April 27, 1998; CL-980320)

Novel glycosyl donors **2d**, **4d** and **6d** bearing an 'acetoxy methoxy' leaving group have been prepared and their utility is shown by coupling them with alcohols **A-G** to obtain di- and trisaccharides by use of BF_3-Et_2O as a promoter.

A revival in oligosaccharide synthesis has been witnessed[1] due to the increased appreciation of the glycoconjugates for the significant role[2] played in eukaryotic biology and disease. Highly practical synthesis of complex oligosaccharides involves coupling (inter- and intramolecular[3]) of a protected glycosyl donor bearing a leaving group at the anomeric centre with a sugar alcohol by use of a suitable activator. Thus, vibrant activity in the designed[4] and serendipitous[5] synthesis of glycosyl donors having a variety of anomeric leaving groups (including those generated *in-situ*[6]) has resulted in the development of several glycosylation methods. Contemporary oligosaccharide synthesis relied upon use of glycosyl donors with a leaving group, rather than those without; for the simple reason that they are easy to prepare, have longer shelf life, allow directed activation (armed-disarmed mode[7]) and offer choice of a wide range of activators and solvents to achieve anomeric diastereoselectivity.

Herein, we report our efforts that culminated in the design, development and ultimately utility of a novel protected glycosyl donor having an 'acetoxymethoxy' group that can be activated either by Lewis or protic acids for the synthesis of saccharides. Thus, in principle a protected glycosyl donor **a** bearing an 'acetoxymethoxy' leaving group, when activated by an acid would generate glycosyloxymethylene carbocation **b** (fission A) (Scheme 1),which on further relay(fission B)should lead to the formation of thermodynamically more stable glycosyl cation **c**, to be captured by a nucleophile (sugaralcohol)to form saccharide **d**.

Thus, the glycosyl acetoxymethoxy donor, (2,3,4,6-tetra-O-benzyl-β- D-glucopyranosyloxy)methylene acetate **2d** was synthesized (Scheme 2) by reaction of β-D-glucopyranose pentaacetate **1a** with propargyl alcohol and BF_3-Et_2O in dichloromethane at room temperature for 2 h to obtain the propargyl glycoside **1b**.[8] Deacetylation (cat. NaOMe/MeOH) followed by benzylation (BnBr/NaH/DMF) of **1b** gave the propargyl derivative **2b**. Reaction of **2b** with Hg $(OCOCF_3)_2$ (0.2 mole equivalent) in 30% aqueous acetone at room temperature for 16 h gave the keto compound **2c**, subsequent Baeyer-Villiger oxidation (m-CPBA/CH_2Cl_2/RT/6 h) gave **2d** in 64.8% overall yield from **1a** as a syrup and was characterized by the ^{1}H-NMR spectrum from the appearance of a methyl group at δ 1.96 and methylenedioxy protons(2 H) at δ 5.4 (dd).^{13}C-NMR spectrum indicated C-1 at δ 101.5, an ester carbonyl at δ 170.1 and methylenedioxy carbon at δ 85.4.[9] IR spectrum showed the ester carbonyl absorption at 1740 cm^{-1}.



Scheme 1.

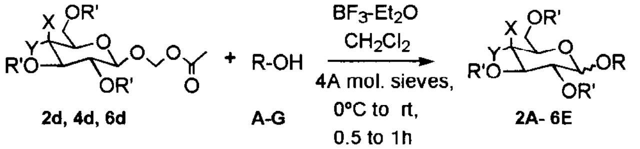
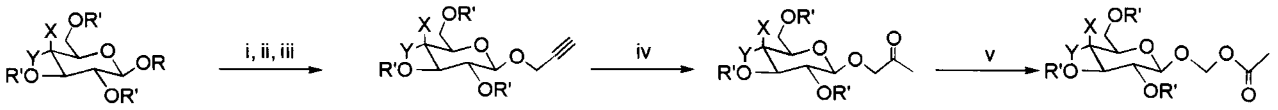


Table 1. Reactions of glycosyl donors **2d**, **4d** and **6d** with various alcohols R-OH (**A-G**) to form saccharides **2A-6E**

Entry	Coupling	Saccharides	α : β ratio	% yield
1	**2d + A**	**2A**	1 : 3	83
2	**2d + B**	**2B**	1 : 1	85
3	**2d + D**	**2D**	1 : 3	72
4	**2d + E**	**2E**	1 : 4	78
5	**2d + F**	**2F**	1 : 3	78
6	**2d + G**	**2G**	1 : 3	75
7	**4d + A**	**4A**	1 : 3	81
8	**4d + C**	**4C**	1 : 1	88
9	**4d + D**	**4D**	1 : 3	77
10	**4d + E**	**4E**	1 : 4	82
11	**6d + D**	**6D**	1 : 3	79
12	**6d + E**	**6E**	1 : 4	80

Coupling of **2d** with highly reactive **B,D,F,G** and hindered alcohols **A,E** in CH_2Cl_2,BF_3-Et_2O at room temperature gave saccharides **2B,2D,2F,2G,2A** and **2E** respectively in good yields (72-88%) (Table 1), where β-glycosides predominated. Likewise, (2,3,4,6-tetra-O -benzyl -β -D - galactopyranosyloxy)-methylene acetate **4d**[10] and the disaccharide donor (2,3,4,6, 2', 3'6'-hepta-



1a : R = Ac, R' = Ac, X = H, Y = OAc
1b : R = Propargyl, R' = Ac, X = H, Y = OAc
3a : R = Ac, R' = Ac, X = OAc, Y = H
3b : R = Propargyl, R' = Ac, X = OAc, Y = H
5a : R = Ac, R' = Ac, X = H, Y =O- (2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-
5b : R = Propargyl, R' = Ac, X = H, Y =O- (2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-

2b : R' = Bn, X = H, Y = OBn
4b : R' = Bn, X = OBn, Y = H
6b : R' = Bn, X = H, Y =O- (2,3,4,6-tetra-O-benzyl-β-D-galactopyranosyl) -

2c : R' = Bn, X = H, Y = OBn
4c : R' = Bn, X = OBn, Y = H
6c : R' = Bn, X = H, Y =O- (2,3,4,6-tetra-O-benzyl-β-D-galactopyranosyl) -

2d : R' = Bn, X = H, Y = OBn
4d : R' = Bn, X = OBn, Y = H
6d : R' = Bn, X = H, Y =O-(2,3,4,6-tetra-O-benzyl-β-D-galactopyranosyl) -

Scheme 2. Reagents and conditions: i: Propargyl alcohol, BF_3-Et_2O, CH_2Cl_2, rt, 2 h, 92-95%, ii: Cat. NaOMe, MeOH, rt, 6 h, iii: NaH, BnBr, DMF, 0°C to rt, 3 h, 90-97%, iv: $Hg(OCOCF_3)_2$, 30% aq.acetone, rt, 16 h, 84-91%,v: m -CPBA. CH_2Cl_2, rt, 6 h, 87-89%.

O-benzyl-β-D-lactopyranosyloxy)methylene acetate **6d**[11] were synthesized from the corresponding peracetates **3a** and **5a** respectively in good yields. Coupling of **4d** with alchols **A, C, D, E** and **6d** with **D** and **E** has resulted in the isolation of saccharides **4A, 4C, 4D, 4E** and **6D, 6E**[12] respectively in good yields (Table1).

In conclusion, we have described synthesis of novel glycosyl donors bearing an acetoxymethoxy leaving group and demonstrated its utility for the synthesis of di- and trisaccharides. Efforts are continuing to optimize reaction conditions, such as change of promoter, solvents and temperature to achieve higher diastereoselectivity in the coupling.

Typical experimental procedure: to a mixture of donor (1 mole equiv.) and acceptor (1.1 mole equiv.) in CH_2Cl_2 (3 ml) at 0 ° C under nitrogen atmosphere was added 4 A° molecular sieves (10 mg) followed by BF_3-Et_2O (1 mole equiv.) and was stirred at RT for 0.5-1 h. When t.l.c. indicated completion of the reaction K_2CO_3 (45 mg) was added, stirred, filtered to remove the solid residue and the filtrate was diluted with CH_2Cl_2 washed with water, organic phase dried (Na_2SO_4) and evaporated to a residue which was purified by column chromatography to obtain the saccharides.

SRG thanks UGC, New Delhi for financial support.

References and Notes

1 P. Fugedi, P.J. Garegg, H. Lohn, and T. Norberg, *Glycoconjugate J.*, **4**, 97 (1987) ; K. Toshima and K. Tatsuta, *Chem. Rev.*, **93**, 1503 (1993); G. J. Boons, *Contemporary Organic Synthesis.*, **3**, 173 (1996).

2 A. Varki, *Glycobiology*, **3**, 97 (1993); R. A. Dwek, *Chem. Rev.*, **96**, 683 (1996).

3 G. Stork, and G. Kim *J. Am. Chem. Soc.*, **114**, 1087 (1992); F.Barresi and O.Hindsgaul, *Can. J. Chem.*, **72**, 1447 (1994); Y. Ito and T. Ogawa, *J. Am .Chem. Soc.*, **119**, 5562 (1997).

4 S. Hanessian, C. Bacquet and N. Lehong,. *Carbohydr. Res.*, **80**, *c*17 (1980); R. R. Schmidt and J. Michel, *Angew. Chem., Int. Ed. Engl.*, **19**, 731(1980).

5 D. R. Mootoo, P. Konradsson, U. Udodong and B. Fraser-Reid, *J. Am. Chem. Soc.*, **110**, 5583 (1988).

6 B.A.Garcia, J. L. Poole, and D. Y.Gin, *J. Am. Chem. Soc.*, **119**, 7597 (1997); H. Uchiro, K. Miyazaki and T. Mukaiyama, *Chem. Lett.*, **1997**, 403.

7 H. B . Mereyala and G.V .Reddy, *Tetrahedron.*,**47**, 6435 (1991).

8 H.B. Mereyala and S.R. Gurrala, *Carbohydr. Res.*, in press.

9 E. Breitmaier, "^{13}C NMR spectroscopy methods and application in organic chemistry," 2nd ed (1978).

10 Spectral data for **4d** : IR (neat) 1742 cm^{-1} ; $[\alpha]_D$ -16.5° (c, 1.0, $CHCl_3$) ; ^1H-NMR (200 MHz, $CDCl_3$) : δ 1.98 (s, 3 H, $OCOCH_3$) 3.42 - 3.95 (m, 6 H, $H_{2\text{-}6}$), 4.3-5.0 (m, 9 H, H_1 and 4x OCH_2Ph), 5.32, 5.51 (d, 2 H, J_{gem}= 7.2 Hz, O-CH_2-O), 7.1-7.4 (m, 20 H, H_{arom}); Selected ^{13}C-NMR data (50 MHz, $CDCl_3$): δ 20.8 ($OCOCH_3$), 85.3 (O-CH_2-O), 101.6 (C_1), 170.2 ($OCOCH_3$).

11 Spectral data for **6d** : IR (neat) 1745 cm^{-1} ; $[\alpha]_D$ 2.06° (c, 1.0, $CHCl_3$) ; ^1H-NMR (200 MHz, $CDCl_3$) : δ 1.95 (s, 3 H, $OCOCH_3$), 3.2 - 4.2 (m, 12 H, $H_{2\text{-}6}$, $H_{2'\text{-}6'}$), 4.1 - 5.1 (m,16 H, $H_{1,1'}$, 7 x OCH_2Ph), 5.28, 5.5 (d, 2 H, J_{gem} = 6.8 Hz, O-CH_2-O), 7.0-7.5 (m, 35 H, H_{arom}); Selected ^{13}C- NMR data (50 MHz, $CDCl_3$): δ 20.8 ($OCOCH_3$), 85.4 (O-CH_2-O), 101.5, 102.7 ($C_{1,1'}$), 170.2 ($OCOCH_3$).

12 All the new compounds gave satisfactory elemental analysis.