Direct Elaboration of Pent-4-enyl Glycosides Into Disaccharides

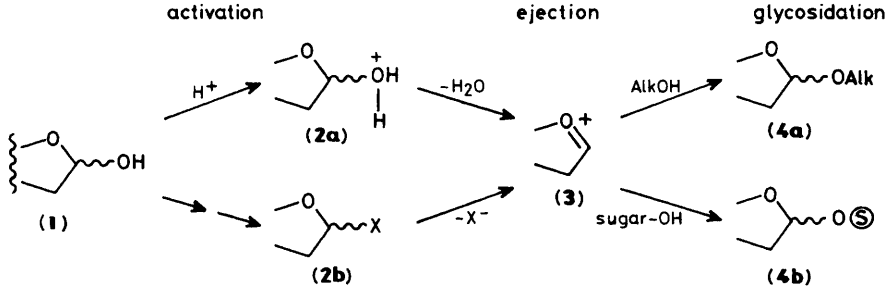
Bert Fraser-Reid,* Peter Konradsson, David R. Mootoo,* and Uko Udodong

Department of Chemistry, Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706, U.S.A.

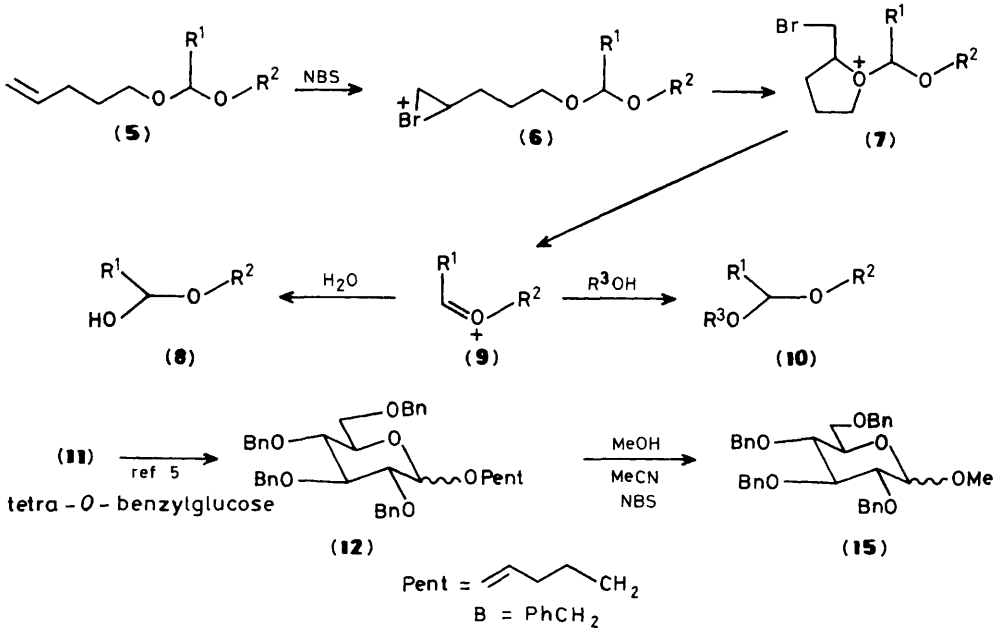
Pent-4-enyl glycosides, on treatment with halonium ions, become chemospecifically activated so that coupling with partially protected monosaccharides can be effected, leading to the *in situ* formation of disaccharides.

Glycosidation, *i.e.* conversion of a glycose (**1**) into a glycoside (**4**), is of crucial importance to all phases of carbohydrate chemistry. When the 'alcohol' reactant is a simple alkyl derivative, excellent protection is provided for the delicate anomeric centre through formation of an alkyl glycoside, *e.g.* (**4a**). Where the alcohol is a protected monosaccharide, the product is a disaccharide, *e.g.* (**4b**). In either case, the anomeric centre of (**1**) must be converted into an electrophile, and this requires activation by development of a good leaving group, and its subsequent ejection to generate the cyclic oxonium ion (**3**).[1] These tandem stages can be accomplished *in situ* [(**1**) → (**2a**) → (**3**)], as in the Fischer glycosidation where simple alkanols, used in generous excess with acidic catalysts, bring about a one-pot transformation, (**1**) → (**4a**).[2] In an alternative, more versatile strategy, the anomeric centre is activated by prior formation of a stable glycosyl derivative (**2b**), from which the ion (**3**) is generated under controlled conditions.[3] This option is particularly appropriate where the alcohol is a precious commodity, *e.g.* a protected sugar alcohol to be used in forming a disaccharide (**4b**). The outline in Scheme 1 makes it obvious that *in situ* transformation of one alkyl glycoside into another, or into a disaccharide, *e.g.* (**4a**) → (**4b**), is inconceivable in the present state of the art, since the available procedures for activating (**4a**) are incompatible with the formation of (**4b**). We report here that pent-4-enyl glycosides undergo ready *in situ* glycoside exchange with simple or complex alcohols under neutral and highly chemospecific conditions.

We reported recently that pent-4-enyl acetals, such as (**5**), undergo oxidative hydrolysis with *N*-bromosuccinimide (NBS) to give the hemiacetal (**8**), or products derived therefrom.[4,5] We suggest that the reaction begins with the reversible formation of the cyclic bromonium ion (**6**), which 'cascades' to an oxolanium (**7**), then an oxonium ion (**9**). An alcohol should then react with the ion (**9**) to afford the acetal (**10**) in an overall process [(**5**) → (**10**)] that would accomplish glycoside exchange. To test this idea, the pent-4-enyl glycoside (**12**) was prepared by Fischer glycosidation of tetra-*O*-

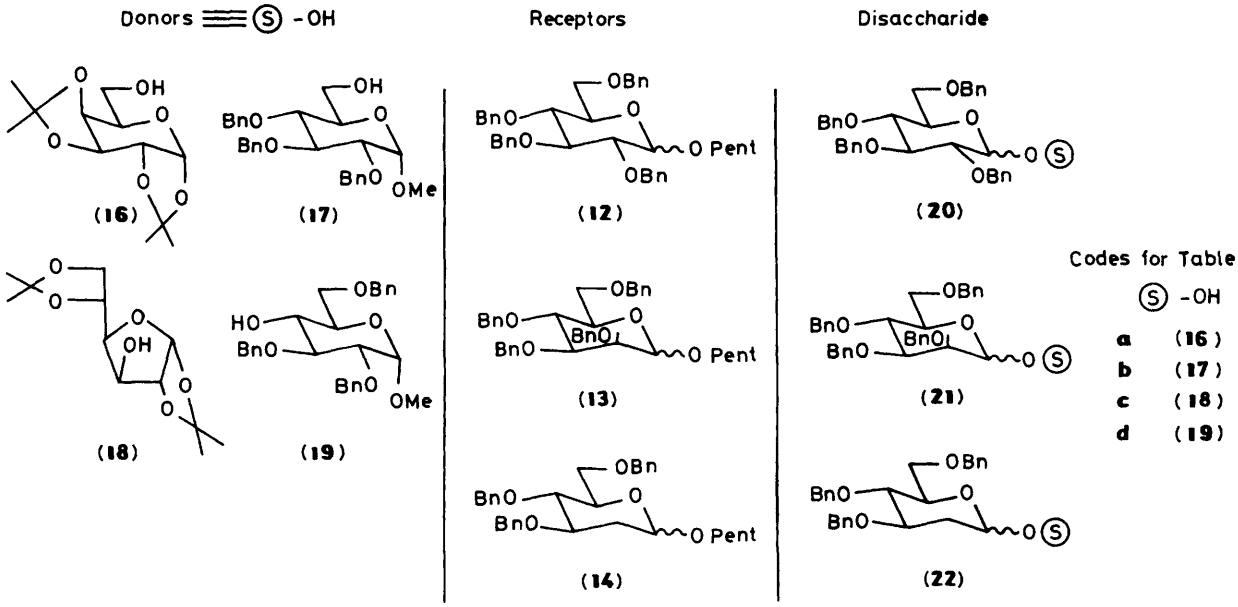


Scheme 1



Scheme 2

Solvent	X⁺ source	Time (h)	Yield (%)	α : β
MeCN	NBS	3	85	1 : 3
MeCN	$I(collidine)_2ClO_4$	0.5	75	1 : 3
CH_2Cl_2	$I(collidine)_2ClO_4$	0.5	85	1.2 : 1
CH_2Cl_2–Et_2O (1 : 4)	$I(collidine)_2ClO_4$	24	75	3 : 1



Scheme 3

benzylglucose (**11**).[6] Reaction of compound (**12**) with NBS in MeCN–MeOH gave an 85% yield of the methyl glucoside (**15**). With (dicollidine)iodonium perchlorate[7] as an alternative source of halonium ion the reaction time was reduced substantially (Scheme 2).

The reaction of the stereochemically pure anomer (**12**α) or (**12**β) in MeCN led to the same product composition. Obviously, it would be advantageous to achieve some stereoselectivity in the glycosidation reaction, and on the basis of a literature survey on saccharide coupling reactions[8] we decided to investigate CH_2Cl_2 and Et_2O as solvents. The iodonium salt was insufficiently soluble in pure Et_2O, and a 4 : 1 mixture of Et_2O and CH_2Cl_2 was adopted. Encouraged by the yields and anomeric stereoselectivities (Scheme 2), we decided to examine the monosaccharide alcohol donors (**16**)—(**19**), as well as the additional receptors (**13**) and (**14**).

Table 1. Disaccharides from pent-4-enyl glycosides.

Entry	Substrate	Solvent[a] (Time/h)	Products from (16)—(19)[b] % Yield (α : β ratio)			
			(20a)	**(20b)**	**(20c)**	**(20d)**
i	**(12)**	A (1—2)	50 (1 : 4)	56 (1 : 4)	20 (2 : 1)	20 (1 : 2)
ii		B (1—2)	66 (1.2 : 1)	93 (1 : 1.4)	58 (3 : 1)	75 (1.2 : 1)
iii		C (16—24)	76 (7 : 1)	96 (7 : 1)	86 (4 : 1)	95 (3 : 1)
			(21a)	**(21b)**	**(21c)**	**(21d)**
iv	**(13)**	A (2—5)	48 (1.3 : 1)	70 (1 : 1)	32 (1.4 : 1)	36 (6 : 1)
v		B (2—5)	71 (1 : 1)	88 (1 : 1)	63 (7 : 1)	76 (9 : 1)
vi		C (24)	70 (2.4 : 1)	94 (1 : 1.3)	79 (α only)	92 (α only)
			(22a)	**(22b)**	**(22c)**	**(22d)**
vii	**(14)**	A (0.5)	61 (2 : 1)	52 (1 : 1)	40 (5 : 1)	51 (7 : 3)
viii		B (0.5)	77 (2 : 1)	73 (1 : 1)	66 (5 : 1)	57 (4 : 1)
ix		C (4—6)	75 (4 : 1)	70 (1 : 1)	65 (5 : 1)	61 (4 : 1)

[a] A = MeCN; B = CH_2Cl_2; C = Et_2O–CH_2Cl_2 (4 : 1). [b] For designation of **a**, **b**, **c**, and **d**, see Scheme 3.

The results (Scheme 3; Table 1) show certain trends that appear to support the following preliminary generalizations:

(a) Comparison of the three groups of entries suggests that the *gluco*-derivative (**12**) [which is a prototype for the equatorial C(2)–O] gives the best α *vs.* β solvent dependence, MeCN favouring β, and Et_2O favouring α (the same trend as noted for MeOH in Scheme 2). For the receptors (**13**) and (**14**), no consistent pattern of solvent dependence has thus far been observed.

(b) With Et_2O as solvent, primary alcohols are much more stereoselective donors than secondary in the case of the *gluco*-receptor (**2**). However, the trend is reversed with the *manno*-derivative (**13**) (*cf.* entries iii and vi).

(c) With the 2-deoxy receptor (**14**), the primary alcohol is stereorandom in all solvents, but secondary alcohols give appreciable α-selectivities [(**22a**)/(**22b**) *vs.* (**22c**)/(**22d**)].

(d) For all receptor–alcohol combinations, MeCN gives the lowest overall yields of disaccharide products. This is due to side reactions which are currently being investigated.

(e) For all receptor–alcohol combinations, CH_2Cl_2 shows the least dramatic anomeric selectivity one way or the other.

2-Deoxy-glycosides, *e.g.* (**14**), are very prone to acid hydrolysis; hence the oxidative deglycosidation is particularly appealing for their manipulations. The results in Scheme 3 show that the reactions of (**14**) are generally much faster than those of either (**12**) or (**13**). This observation parallels the generally observed trends in acid lability of the three receptors.

We are grateful to the National Science Foundation (CHE 8703916) and Glaxo, Incorporated (Research Triangle Park, North Carolina) for financial support.

Received, 23rd February 1988; Com. 8/00703I

References

1 For a condensed account of the Koenigs-Knorr reaction, see A. F. Bochkov and G. E. Zaikov, 'Chemistry of the *O*-Glycosidic Bond: Formation and Cleavage,' Pergamon, New York, 1979.
2 B. Capon, *Chem. Rev.*, 1969, **69**, 407.
3 See, for example: K. C. Nicolaou, A. Chucholowski, R. E. Dollie, and J. L. Randall, *J. Chem. Soc., Chem. Commun.*, 1984, 1155; K. C. Nicolaou, T. Ladduwahetty, J. L. Randall, and A. Chucholowski, *J. Am. Chem. Soc.*, 1986, **108**, 2466; S. Hanessian and Y. Guindon, *Carbohydr. Res.*, 1980, **86**, C3; R. R. Schmidt, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 212.
4 D. R. Mootoo, V. Date, and B. Fraser-Reid, *J. Chem. Soc., Chem. Commun.*, 1987, 1462.
5 D. R. Mootoo, V. Date, and B. Fraser-Reid, *J. Am. Chem. Soc.*, 1988, **110**, 2662.
6 O. T. Schmidt, T. Aver, and H. Schmadel, *Chem. Ber.*, 1960, **93**, 556.
7 D. E. Iley and B. Fraser-Reid, *J. Am. Chem. Soc.*, 1975, **97**, 2563; B. Fraser-Reid and D. E. Iley, *Can. J. Chem.*, 1979, **57**, 645; R. U. Lemieux and A. R. Morgan, *ibid.*, 1965, **43**, 2190.
8 For leading references, see: Y. Ito and T. Ogawa, *Tetrahedron Lett.*, 1987, **28**, 4701.