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One pot/two donors/one diol give one differentiated trisaccharide: powerful evidence for reciprocal donor–acceptor selectivity (RDAS)

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Three component, one-pot reactions involving equimolar amounts of the acceptor diol and both armed and disarmed donors presented simultaneously, produce a *single* double-differential glycosidation product; this phenomenon provides evidence for Reciprocal Donor Acceptor Selectivity (RDAS).

The traditional protocol for differential, double-glycosidation of an acceptor diol requires a series of programmed protection/deprotection steps to ensure that only one of the acceptor-OHs is presented to each donor at each coupling event.[1,2] Thus, for the case illustrated in equation (i), a *minimum* of four steps would be needed to obtain compound **3** from diol **1**, without contamination of the diastereomer **4** (and avoidance of the symmetrical competitors **5** and **6**). The direct process, **1**→**3**, is generally thought to require exquisite regioselective finesse and therefore is best left to enzymatic procedures.[3]

However, in this manuscript, we report the development of differential, double-glycosidations of diols in which donors are virtually 'told' where to go, thereby enabling direct conversions of the type **1**→**3**, without contamination of regioisomer **4**.

We recently reported that a variety of diols, including **7**, **8** and **9**, underwent regioselective glycosidations upon treatment with *n*-pentenyl glycosyl donors.[4] Thus, a disarmed donor (NPG_{BZ}), *e.g.* **10**, and/or its orthoester (NPOE) equivalent, *e.g.* **11**, glycosidated the bold **OH** overwhelmingly (and frequently exclusively)[5] whereas the armed donor, *e.g.* **12**, was promiscuous, reacting substantially with both italic and bold-OHs.

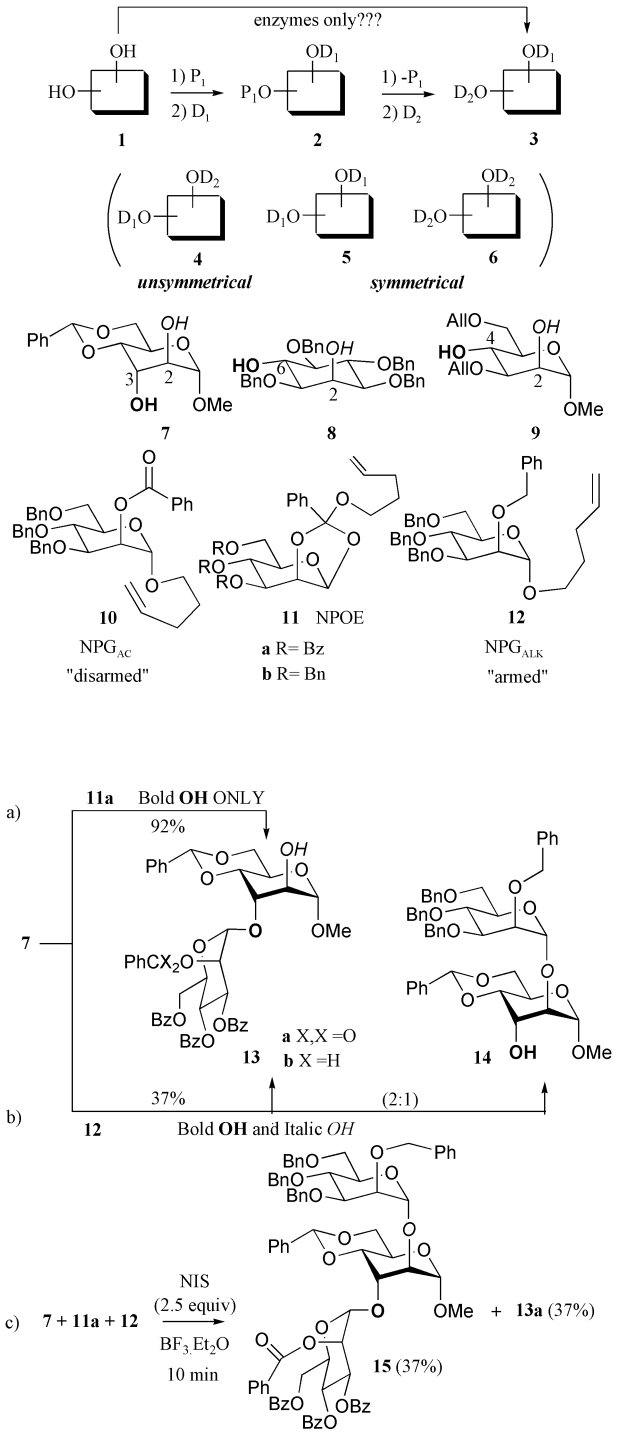
Clearly, these examples indicate that each donor expresses preference for one of the diol –OHs and *vice versa*, the resulting 'match' being evidence for *Reciprocal Donor Acceptor Selectivity (RDAS)*.† [6] A rationalization for these selectivities awaits further insight; but their reality invites immediate practical exploitation.

For in-depth studies, we chose to first examine altroside **7**. This diol had given a 92% yield of **13** as the exclusive product with NPOE **11a**, but a 2 : 1 mixture of **13b** and **14** with the armed NPG_{ALK} **12**[4] [Scheme 1 (a and b)]. Notably the preferred site for *both* donors is the bold (C3)-**OH** which, on the basis of conventional wisdom, did not augur well for differential, double-glycosidation experiments.

Nevertheless, when a 1 : 1.3 : 1.3 mixture of diol **7**, and both donors, (**11a** and **12**) was treated with 2.5 equivalents of NIS and a catalytic amount of $BF_3{\cdot}Et_2O$ for 10 min, trisaccharide **15** and disaccharide **13a**, were obtained as the only products in 37 and 37% yields respectively.

Obviously, the yield of trisaccharide **15**, would be improved if glycosidation of disaccharide **13a** by NPG_{ALK} donor **12** could be enhanced. Indeed, entries i→iv in Table 1 show that increasing the concentration of the armed donor **12**, had a salutary effect on the yield of **15**.

An even more interesting set of results arises from our studies on diol **16** (Scheme 2). Differential 3,6-dimannosylation of this mannoside is of interest since the resulting trimannan occurs as



Scheme 1 Glycosidation of altroside **7** with glycosyl donors **11a** and **12**.

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Table 1 One-pot glycosidation of altroside**7** with donors **11a** and **12**.

Entry	**7** (equiv.)	**11a** (equiv.)	**12** (equiv.)	**15**[a] (%)	**13a** (%)
i	1	1.3	1.3	37	37
ii	1	1	1.6	43	31
iii	1	1	2	52	19
iv	1	1	3	57	16

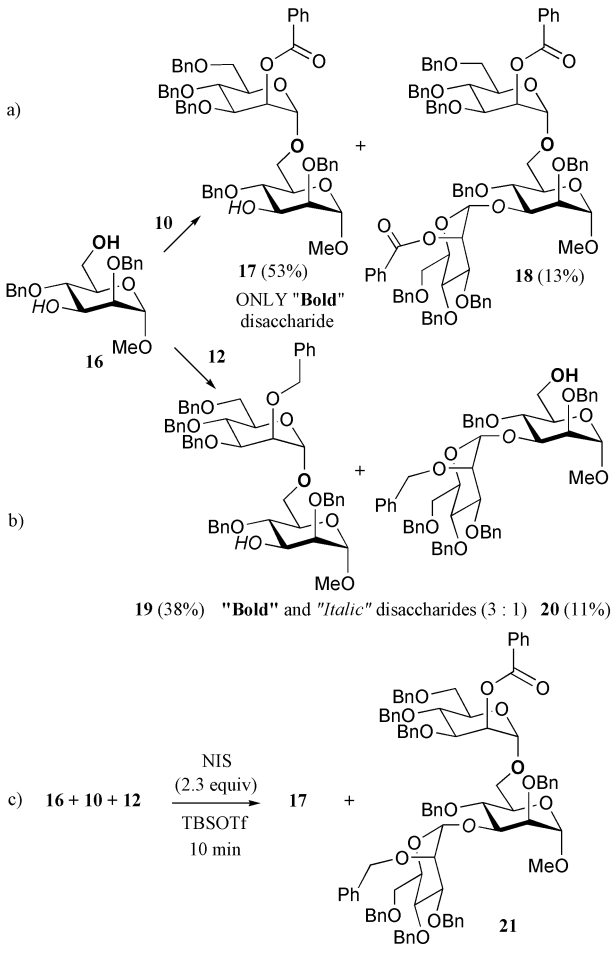
[a] Compound **15** is the *only* trisaccharide (of four possibilities) observed in these optimizations.

a repetitive, interlocking motif in high mannose glycoproteins.[7]

The RDAS preferences of **16** were determined by the previously described equimolar two-component reactions‡ shown in Scheme 2 (a and b). With the disarmed donor **10**, mannosylation occurred at the bold (C6)-**OH** only to give **17** in 53% yield, and also the symmetrical trisaccharide **18** in 13% yield—but with *no* evidence (TLC nor NMR) for the dimannan resulting from glycosidation of the italic (C3)-*OH*. By contrast, the 'armed' donor **12** gave a 38% yield of the **O**6 product, **19**, but also 11% of the *O*3 regioisomer **20**.

Analysis of the results in Scheme 2 (a and b) according to conventional wisdom, dictates that the preference of both donors, **10** and **12**, for the primary –OH 'is to be expected' on the grounds of steric hindrance, and so in contemplating a differential, double-glycosidation experiment, the obvious question was: What will happen when **10** and **12** compete for diol **16**? Our calculations[8] showed that the relative reactivity of these donors (k_{12}/k_{10}) is 3.2. Hence, it was expected that O6 mannosylation by the 'armed' donor, **12**, would predominate in any trimannan produced.

Surprising disagreement with conventional wisdom is depicted in Scheme 2(c). Thus the 1:1:1 three-component

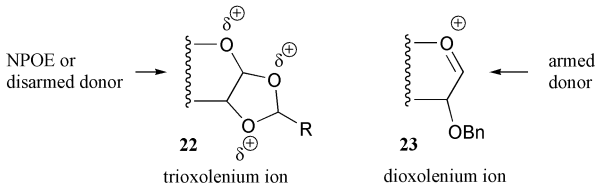


Scheme 2 Glycosidation of mannoside **16** with donors **10** and **12**.

Table 2 One-pot glycosidation of mannoside **16** with donors **10** and **12**.

Entry	**16** (equiv.)	**10** (equiv.)	**12** (equiv.)	**17**[a] (%)	**21**[a] (%)
i	1	1	1	36	21
ii	1	1	2	27	25

[a] Compound **22** is the *only* trisaccharide (of four possibilities) observed in these optimizations.



Scheme 3

reaction of **10**, **16** and **12** (entry i) gave a single trimannan **22**, in which the *less* reactive donor **10** ended up at **O**6. But even more surprisingly, the same held true for the single disaccharide, **17**, obtained.As with the altroside study in Scheme 1, an increase in the ratio of the armed donor **12** (entry ii) led to an increase (albeit modest) of trisaccharide **21**—but still *none* of the symmetrical trisaccharide.

In reviewing the above data, we regard it as simply astonishing that even with the audacious disparity in the ratio of donors **12** and **11a** (Table 1, equation iv) or **12** and **10** (Table 2, equation ii), there was absolutely *no* evidence for trisaccharides other than **15** and **21**. In view of the excess of the 'armed' donor **12** in these experiments, symmetrical dimannosylation was expected in both Schemes 1 and 2.

A study[8] of the three types of *n*-pentenyl donors used above indicate that their relative reactivities are in the order NPOE > armed > disarmed (*e.g.* **11** > **12** > **10**). The most and least stable donors therefore give rise to the highly delocalised, more stable intermediate **22**, while the armed donor gives the less stable oxocarbenium ion **23**[9] (Scheme 3). The conclusion from Scheme 1(c) and Scheme 2(c) is that in *competitive* glycosidations, the more stable donor/*intermediate* (not the most *reactive* donor) controls regioselectivity, resulting in the formation of the single trisaccharides **15** and **21** and the single disaccharides **13a** and **17**. How the competing OH groups play into this phenomenal regioselectivity awaits clarification.

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Notes and references

† The *regio*selectivities are the same whether the NPOE or NPG_{BZ} is used, although yields and side-products may differ.

‡ The structure of the regioisomers was determined, as previously described.[4]

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