Lanthanide Triflates/*N*-Iodosuccinimide for Chemoselective Coupling of *n*-Pentenyl Donors in Oligosaccharide Assembly

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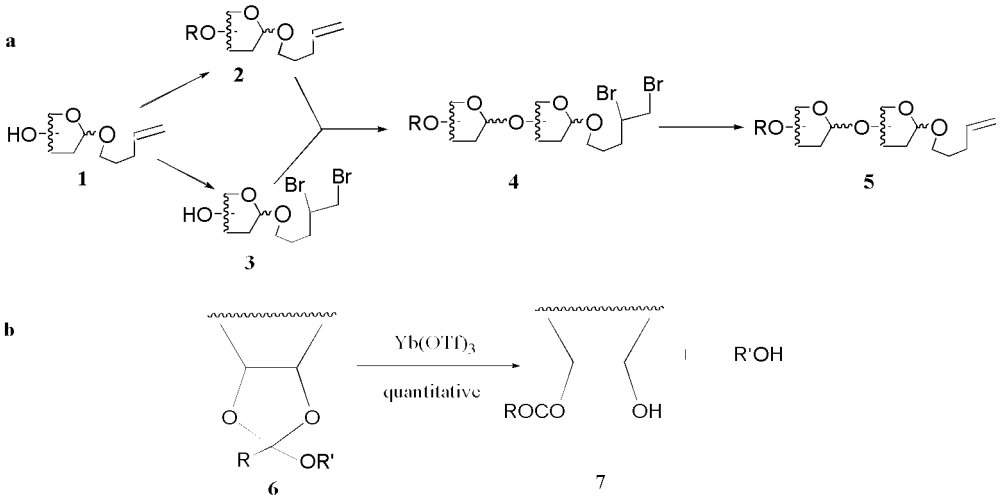
Abstract: Armed *n*-pentenyl glycosides (NPGs) react (a) readily with scandium and indium (III) triflates, (b) moderately with samarium and lanthanum counterparts, and (c) not at all with ytterbium counterpart. However the last salt reacts readily with *n*-pentenyl orthoesters (NPOE). These chemoselectivities of *n*-pentenyl donors towards lanthanide salts therefore permit hydroxyl-bearing armed NPGs to function as acceptors towards NPOE donors. This concept is demonstrated by synthesis of a tetrasaccharide.

Key words: lanthanide triflates, *N*-Iodosuccinimide, *n*-pentenyl glycosides

Protecting groups are a necessary evil in the synthesis of complex oligosaccharides. It is therefore a worthwhile objective to convert this defect into an advantage to enhance stereo, chemo, and regioselective outcomes. A parallel and complementary aim is to reduce the number of discrete key starting materials that must be furnished in order to execute the synthetic plan. An early strategy for the latter aim is exemplified in Scheme 1.[1] A portion of an NPG, **1,** is protected to obtain a donor, **2**, while another portion is dibrominated to obtain an acceptor, **3**. Coupling of both under the agency of iodonium ion affords a product, **4**, which upon subsequent debromination[2] regenerates the double bond in **5**. The latter is now ready to serve as a donor. This protocol enables efficient use of **1**, and the strategy has been used to advantage in reports from our laboratory.[3]

Nevertheless, protection/deprotection episodes, even as mild as those in Scheme 1a, can never be taken for granted and hence are best avoided. Chemoselective processes provide one solution. Thus, one can rely on differences in the glycon, as in armed/disarmed strategies,[4,5] latent/active,[6] orthogonal,[7] semi-orthogonal,[8] or in the aglycon.[9] In this manuscript, we describe a process in which the chemoselectivity relies on the nuanced reaction of lanthanide salts with various *n*-pentenyl glycosyl donors.

We recently reported that orthoesters[10] can be efficiently rearranged to β-hydroxy esters, e.g. **6** → **7,** by treatment with ytterbium (III) triflate (Scheme 1b). On the other hand, with an *n*-pentenyl orthoester (NPOE) such as **8** (Scheme 2), the reaction leads to a disarmed *n*-pentenyl glycoside (NPG)[11] **9**. The process is known[12] to go through a dioxolenium ion, **12**[13,14] by loss and reattachment of *n*-pentenyloxy anion. The reverse process is also well established, in that disarmed NPG **9** can generate dioxolenium ion **12** via the oxocarbenium ion **13**.



Scheme 1

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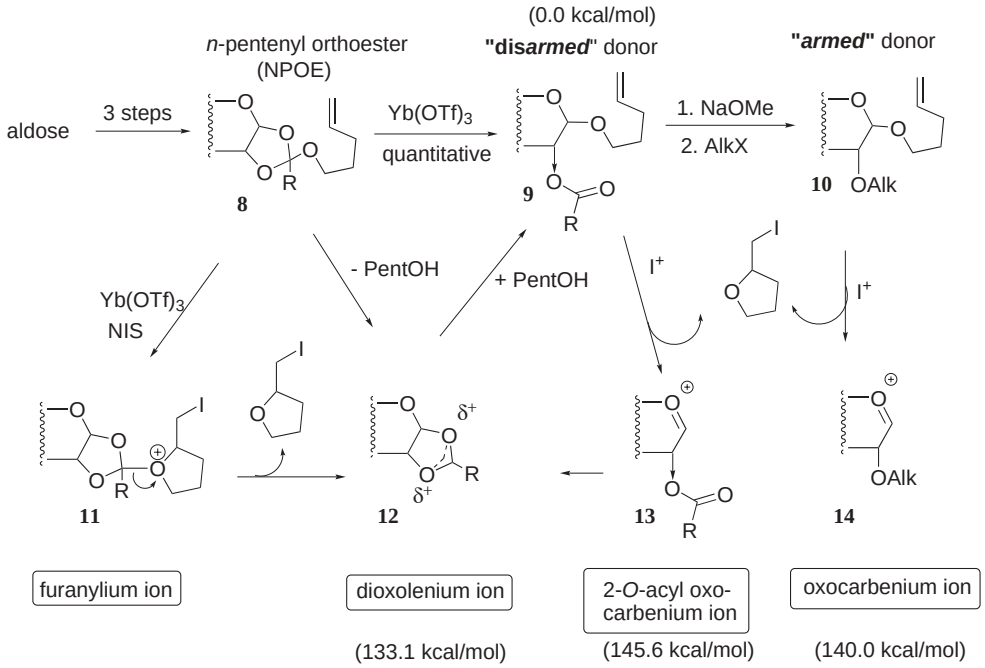
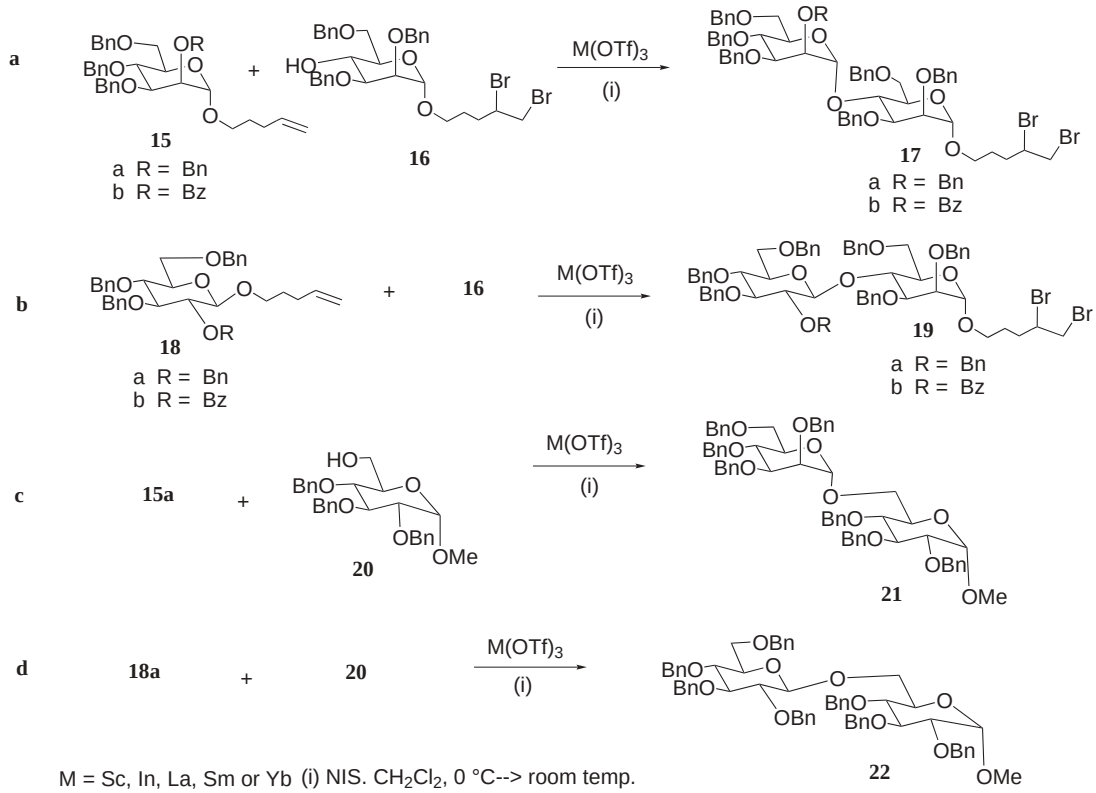


Scheme 2

The high reactivity of glycosyl orthoesters vis a vis 'ordinary' donors is evident in the studies of Kochetkov and co-workers,[15] and our protocol for comparing donor reactivities,[16] show that an NPOE, **8,** is infinitely more reactive than the corresponding disarmed NPG, **9**; and as is well known, the latter is less reactive than the armed counterpart **10.** The order therefore is: **8** >>>> **10** >> **9.** Further support for this ranking has come from recent high level calculations[14] which yield the transition energies shown in brackets against the appropriate structures in Scheme 2, 133.1 kcal/mol, 140.0 kcal/mol and 145.6 kcal/mol for dioxolenium >>>> armed >> disarmed intermediates.



Scheme 3

Table 1 Reaction of Acceptor **16** with Armed and Disarmed *n*-Pentenyl Glycosides under the Agency of Lewis Acids and *N*-Iodosuccinimide[17,18]

Entry	Lewis acid	Donor	Time	Product	Yield (%)
i	$Sc(OTf)_3$	**15a**	30 min	**17a**	98
ii		**18a**	30 min	**19a**	89
iii		**15b**	15 min	**17b**	92
iv		**18b**	20 min	**19b**	78
v	$In(OTf)_3$	**15a**	50 min	**17a**	96
vi		**18a**	50 min	**19a**	97
vii		**15b**	30 min	**17b**	91
viii		**18b**	30 min	**19b**	86
ix	$Sm(OTf)_3$	**15a**	24 h	**17a**	23
x		**18a**	24 h	**19a**	54
xi		**15**	36 h	–	No reaction
xii		**18b**	36 h	–	No reaction
xiii	$La(OTf)_3$	**15a**	24 h	–	No reaction
xiv		**118**	24 h	**19a**	37
xv		**15b**	36 h	–	No reaction
xvi		**18b**	36 h	–	No reaction
xvii	$Yb(OTf)_3$	**15a**	36 h	–	No reaction
xviii		**18a**	36 h	–	No reaction
xix		**15b**	36 h	–	No reaction
xx		**18b**	36 h	–	No reaction

The results with $Yb(OTf)_3$ encouraged us to explore the use of this,[11] and other lanthanide salts, as Lewis acid surrogates to generate iodonium ion (I^+) from *N*-iodosuccinimide (NIS) for activating *n*-pentenyl donors.

We found that coupling of the armed donor **15a** with the dibrominated NPG acceptor **16**,[3] occurred readily with scandium (III) and indium (III) triflates at to give disaccharide **17a** (Scheme 3) in near quantitative yields (Table 1, entries i and v). With the corresponding samarium salt, the coupling was uselessly slow, being incomplete after 24 hours at room temperature (Table 1, entry ix). The lanthanum and ytterbium counterparts (Table 1, entries xiii and xvii) failed to induce any reaction even after 24 hours and 36 hours, respectively, at room temperature.

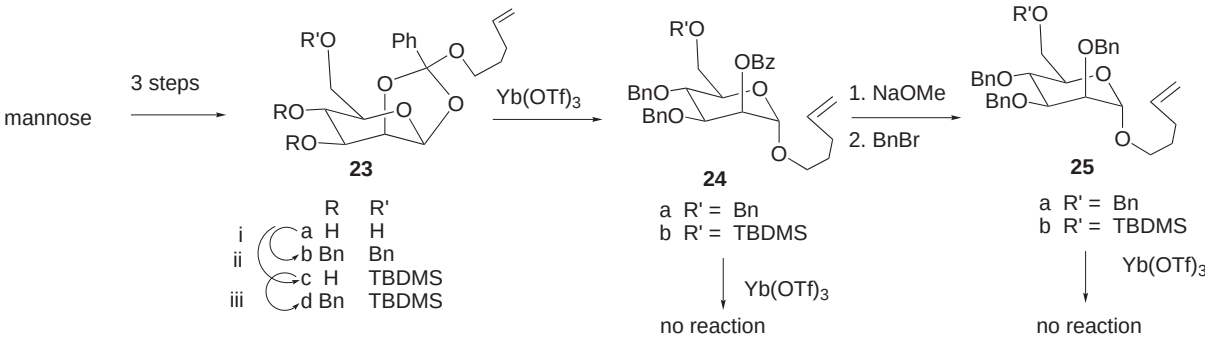
It was of interest to determine whether the foregoing results were specific to donor **15a**, since the high anomeric effect of such α-mannosides[19] confers substantial protection against electrophile-induced activation. The β-glucoside **18a**, was therefore examined. Table 1 shows that the only difference with the mannoside **15a** is with respect to the lanthanum salt, in that the glucoside gives some disaccharide, **19a** (Table 1, entries xiii vs. xiv).

The disarmed, 2-O-benzoyl *manno* and *gluco* counterparts **15b** and **18b** were next tested and found to behave similarly towards the acceptor **16**. Thus scandium and indium triflates induced smooth coupling at 0 ºC (Table 1, entries iii/iv and vii/viii) while samarium, lanthanum and ytterbium triflates were ineffective, even after 36 hours at room temperature (Table 1, entries xi vs. xii, xv vs. xvi and xix vs. xx).

Were the results in Table 1 due to the hindered nature of the C4-OH in acceptor **16**. In order to answer this question, acceptor **20** with a primary-OH was examined

Table 2 Reaction of Acceptor **20** with Armed *n*-Pentenyl Glycosides under the Agency of Lewis Acids and *N*-Iodosuccinimide[17]

Entry	Lewis acid	Donor	Time	Product	Yield (%)
i	$In(OTf)_3$	**15a**	20 min	**21**	94
ii		**18a**	20 min	**22**	93
iii	$La(OTf)_3$	**15a**	24 h	**21**	20
iv		**18a**	24 h	**22**	40
v	$Sm(OTf)_3$	**15a**	24 h	**21**	30
vi		**18a**	24 h	**22**	58
vii	$Yb(OTf)_3$	**15a**	36 h	–	No reaction
viii		**18a**	24 h	–	No reaction

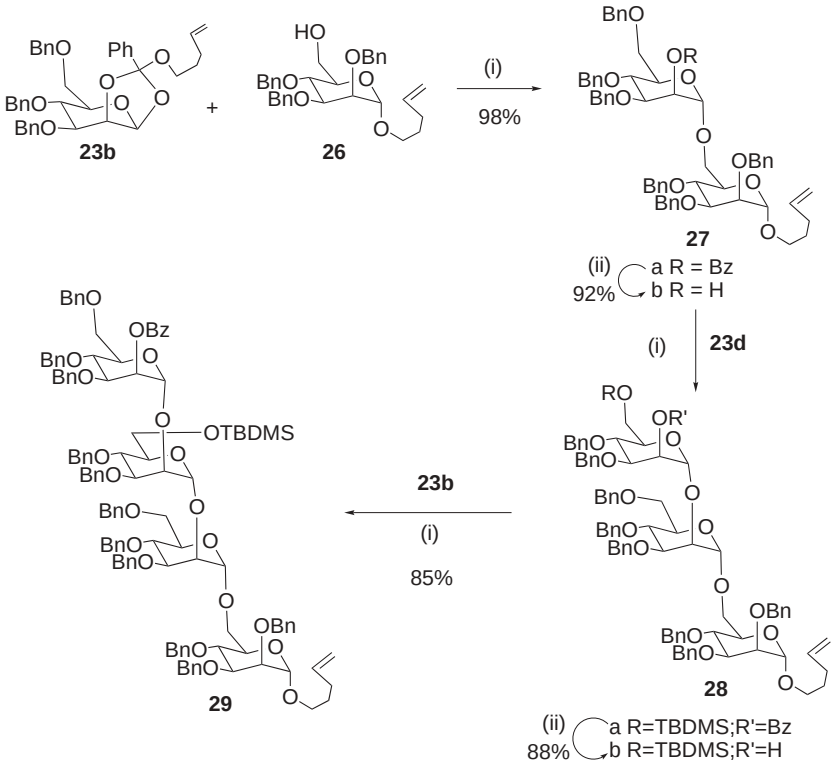


Scheme 4

(Schemes 3c and 3d). The sample results in Table 2 for several salts, show that the selectivities do not appear to be based on steric hindrance. Thus indium triflate gave excellent yields of disaccharides **21** and **22,** lanthanum and samarium triflates moderate yields, while ytterbium triflate failed to promote any coupling.

The subtle selectivities in Tables 1 and 2 encouraged attempts to use these salts as chemoselective agents with *n*-pentenyl donors, that would complement the electronic, and torsional armed/disarmed strategies currently used in oligosaccharide syntheses.[20] Apart from being the only type of 1,2-orthoesters currently in use as glycosyl donors, NPOEs allow ready deployment of different protecting groups. Thus, triol **23a**, was either directly benzylated to obtain **23b,** or selectively protected, rearranged and then processed routinely to obtain the disarmed and then armed NPGs **24** and **25** respectively.

The function of the salt in these couplings is to generate IOTf, the concentration of which is tied to the Lewis acidity of the salt. Being a comparatively mild salt $Yb(OTf)_3$ generates a concentration of IOTf that is sufficient for the transition energy of an NPOE, but not an NPG (Scheme 2). Thus when NPGs **24** and **25** were treated independently with *N*-iodosuccinimide and ytterbium(III) triflate, both were recovered unchanged. These results suggested that armed or disarmed NPGs could serve as acceptors towards orthoester donors. The feasibility of this strategy was demonstrated as shown in Scheme 5. The



(i) NIS, $Yb(OTf)_3$, CH_2Cl_2; (ii) NaOMe, MeOH, CH_2Cl_2

Scheme 5

acceptor alcohol **26** and NPOE **23b** upon treatment with NIS and ytterbium triflate in CH_2Cl_2 at 0 ºC afforded the dimannan **27** in 98% yield. Debenzoylation afforded alcohol **27b**, which was coupled, under the agency of ytterbium triflate, with orthoester **23d** to give **28**. A repeat of the debenzoylation (to give **28b**) and then reuse of **23b** afforded tetramannan **29**.

In summary, the data in Tables 1 and 2 show that armed *n*-pentenyl glycosides (NPGs) react (a) readily with scandium and indium (III) triflates, (b) moderately with samarium and lanthanide counterparts, and (c) not at all with ytterbium counterpart. On the other hand we have previously shown that ytterbium triflate reacts readily with *n*-pentenyl orthoesters (NPOE). These chemoselectivities of *n*-pentenyl donors towards lanthanide salts therefore permit hydroxyl-bearing armed NPGs to function as acceptors towards NPOE donors. This concept is demonstrated in Scheme 4 by synthesis of tetrasaccharide **29**.

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(17) A typical procedure for the glycosidation is as follows: Acceptor (1 equiv) and and *n*-pentenyl donor (3 equiv) were dissolved together in a small amount of toluene and azeotroped to dryness. The residue was dried overnight under vacuum, and then dissolved in anhyd CH_2Cl_2 (5 mL) at 0 °C under Ar atmosphere. NIS (4 equiv) was added to the solution and after stirring for few minutes, the Lewis acid (0.3–0.5 equiv) was added and slowly warmed to r.t. The reaction was monitored by TLC, and when complete, quenched with $NaHCO_3$ and sodium thiosulfate solutions. The organic layer was extracted with CH_2Cl_2, washed with water, and dried over Na_2SO_4. The solvents were removed, and the residue was purified by column chromatography.
(18) When 1.3 equiv of donor were used, the yields with **15a, 15b,** and **18a** fell to 50%, 75% and 74%, respectively.
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