Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 1417–1420

TETRAHEDRON LETTERS

Thioglycoside and trichloroacetimidate donors in regioselective glycosidations. Comparison with *n*-pentenyl glycosides

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Received 13 September 2002; revised 16 December 2002; accepted 19 December 2002

Abstract—Thioglycoside and trichloacetimidate donors show the same regiopreferences as NPG analogs for selective glycosidation of an altroside diol, indicating that the selectivity may be general for donors. They also undergo one-pot, double-differential-glycosidations to give a single trisaccharide out of four possibilities. © 2003 Published by Elsevier Science Ltd.

A recent publication from our laboratory reported remarkable regioselectivities in glycosidations of acceptor-diols based on the *O*2 'protecting groups' of *n*-pentenyl glycosyl donors.[1] In general 'disarmed' 2-*O*-acyl *n*-pentenyl (NPG_{AC}) donors, e.g. **1**, and/or their *n*-pentenylorthoester (NPOE) equivalents, e.g. **2**, are overwhelmingly (and frequently completely) regioselective, while their 'armed' 2-*O*-alkyl (NPG_{ALK}) counterparts, e.g. **3**, are much less discriminating.[2] As a case in point (Scheme 1(a)), treatment of the tetra-*O*-benzyl inositol **4** with 1 equiv. of **1** or **2** gave the *O*6 mannosylation product **5** exclusively, while the NPG_{ALK} donor **3** led to a 1:4 mixture of regioisomers **6** and **7** (Scheme 1(b)).[1,3]

Even more surprising are the results of the one-pot, differential-double-glycosidation, three-component-reaction summarized in Scheme 1(c), in which 1:1:1 mixture of **2a**, **3**, and **4** was presented with 2.6 equiv. of NIS and a catalytic amount of TBDMSOTf.[4] First, a single *pseudo*-trisaccharide, **8**, was obtained in which each donor had gone to its preferred-OH, as revealed in the two-component test reactions (Scheme 1(a),(b)). Second only a single *pseudo*-disaccharide, **5**, was obtained. A search of the detritus of the reaction failed to reveal any other coupling products (such as **6**).

We have thus far used only *n*-pentenyl donors in order to provide a level playing field for our comparisons. Can these observations be extended to other donors, as was the case with the armed/disarmed protocol[4] for oligosaccharide assembly that had been discovered with NPGs[5] and then generalized?[6] Notably, the *n*-pentenyl group of donors is the only one that has orthoesters, e.g. **2**, as functional alternatives to their disarmed counterparts, e.g. **1**.[7]

We therefore decided to test thioglycosides,[8] **9a**,**b**, and glycosyl trichloroacetimidates,[9] **9c**,**d**, which are currently two of the most widely used donors (Scheme 2). For the candidate diol, we chose the altroside **10** which reacted (a) with NPOE **2b** to give the *O*3 disaccharide **11a** exclusively in 92% yield, and (b) with armed NPG_{ALK} **3** to give a 2:1 mixture of **11b** and **12** in 37% combined yield (Table 1, entries i and ii).

Treatment of diol **10** with 1 equiv. of the tetra-*O*-benzoyl thiophenyl donor **9a** (Scheme 3) and NIS/$BF_3{\cdot}OEt_2$ at −30°C afforded a 58% yield of **11a** as the only disaccharide (Table 1, entry iii). By contrast, use of the tetra *O*-benzyl analog **9b**, gave a 2:1 mixture of regioisomers **11b** and **12** in 66% yield (Table 1, entry iv). Therefore, these regiopreferences compare very well with those for NPG donors **2b** and **3** in entries i and ii in Table 1.

At −30°C the reactions of the disarmed trichloroacetimidates, **9c**, were accompanied by appreciable benzylidene migration to the 3,4-*O* position, and so we decided to lower the temperature to −78°C. This had a salutary effect for there was now exclusive *O*3 regioselectivity as with the other two donors (Table 1, entry v). With the armed counterpart **9d**, the lower temperature also benefited the yield (Table 1, entry vi versus vii, while maintaining the 2:1 ratio of products).

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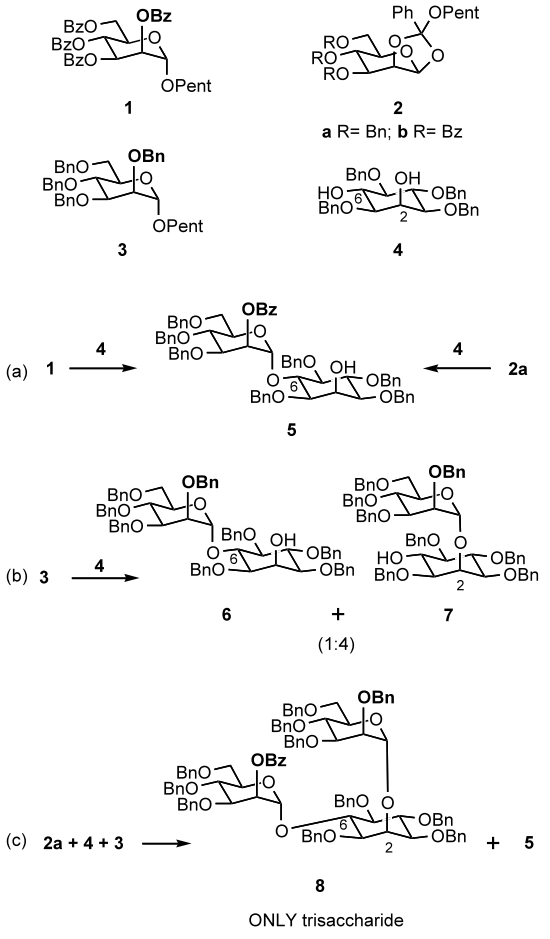
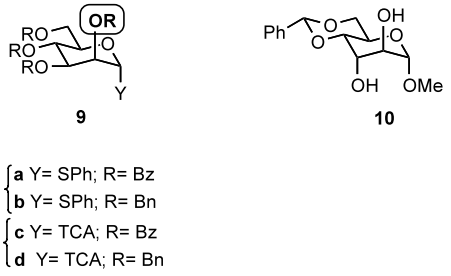
PII: S0040-4039(02)02878-2

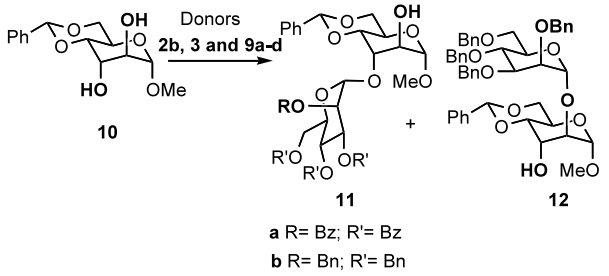


Scheme 1.

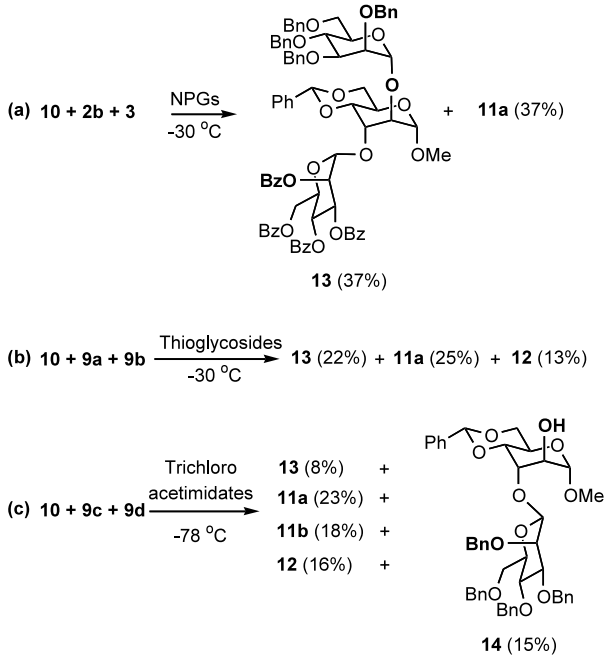


Scheme 2.

We next tested for differential double glycosidations where both donors were presented simultaneously to the diol and allowed to choose their destinations. The



Scheme 3. Regioselectivities in 1:1 two-component glycosidations.



Scheme 4. Differential double glycosidations in 1:1:1 three-component-reactions.

NPGs (Scheme 4(**a**)) gave a 1:1 mixture of compounds **13** and **11a** in 74% overall yield. The thioglycosides gave both products in the same ratio, but also produced disaccharide **12** from the reaction of the armed donor.

The trichloroacetimidates were tested only at −78°C in view of the data in Table 1 (entries v–vii). Only one trisaccharide, **13**, was produced, although there was a rich mixture of disaccharides.

Table 1. *n*-Pentenyl, thioglycoside and trichloroacetimidate donors in regioselective glycosylations

Entry	Donor	Promoter	Temp. (°C)	Products	Ratio *O*3:*O*2	Yield (%)
i	**2b**	NIS/$BF_3{\cdot}Et_2O$	−30	**11a** only	1:0	92
ii	**3**	NIS/$BF_3{\cdot}Et_2O$	−30	**11b**+**12**	2:1	37
iii	**9a**	NIS/$BF_3{\cdot}Et_2O$	−30	**11a** only	1:0	58
iv	**9b**	NIS/$BF_3{\cdot}Et_2O$	−30	**11b**+**12**	2:1	66
v	**9c**	$BF_3{\cdot}Et_2O$	−78	**11a** only	1:0	65
vi	**9d**	$BF_3{\cdot}Et_2O$	−30	**11b**+**12**	2:1	40
vii	**9d**	$BF_3{\cdot}Et_2O$	−78	**11b**+**12**	2:1	54

The above results cannot be accommodated by easy rationalizations based on conventional dogma such as 'steric hindrance' or 'more versus less reactive' concepts. With respect to the diols this is apparent from the range of substrates tested.[1–3] With respect to the donors, using our recently described protocol for measuring relative reactivity,[10] we have shown that for *n*-pentenyl derivatives, the order is generally NPOE> armed>disarmed. Hence the most and least reactive donors target the same OH.

The most surprising development comes from the three-component-reactions. Thus, in Scheme 4(a) and (b), the major products, **13** and **11a**, arise from coupling of the disarmed donors and, in Scheme 4(c), the combined yields from disarmed (**11a**+**13**) and armed (**11b**+**14**) couplings at *O*3 are comparable (31 and 33%, respectively). This outcome is at odds with the data in Table 1 (entries ii, iv and vi/vii) showing that *O*3 is also preferred by the armed donors which, being the 'more reactive', should have given rise to appreciable amounts of disaccharide **11b** (evidently, at −78°C activation of the disarmed trichloroacetimidate, **9c**, is slowed down so much that the armed alternative, **9d**, now has a chance to compete).

The implication from Scheme 4, supported by the extraordinary regioselectivities in Table 1 (entries i, iii and v), is that the disarmed donor and *O*3-OH are a 'matching' pair. The same holds for donors **1**/**2a** and the *O*6-OH in Scheme 1(c). We suggest that the notion of 'matching' between donors and acceptors, that was adumbrated by Paulsen as an intuitive cum empirical concept,[11] is exemplified in these results.[12–15]

Acknowledgements

Funding from the Dirección General de Enseñanza (grants PB97-1244, PPQ2000-1330, and BQU2001-0582) is gratefully acknowledged. C.U. thanks the Comunidad Autónoma de Madrid for a postdoctoral fellowship. B.F.R. is grateful to the Human Frontier Science Program Organization and Synthon Chiragenics of Monmouth Junction, NJ, USA, for partial support of this work.

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9. See for example: Schmidt R. R. In *Modern Methods in Carbohydrate Synthesis*; Khan, S. H.; O'Neil, R. A., Eds; Harwood Academic: The Netherlands, 1996; pp. 20–54 and references cited therein.
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11. Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155–173.
12. *General glycosidation procedure for thioglycoside and n-pentenylorthoester donors*: The diol (0.16 mmol) and the glycosyl donor(s) (0.16 mmol) were dissolved in anhydrous CH_2Cl_2 (3 mL) under an argon atmosphere. Molecular sieves 5 Å (1 mg/mg donor) and *N*-iodosuccinimide (3 equiv./donor) were added at −30°C. After stirring the mixture for 5 min, $BF_3{\cdot}OEt_2$ (0.048 mmol) was added. The reaction was quenched after 15 min with 10% aqueous sodium thiosulphate and saturated aqueous sodium bicarbonate, extracted with dichloromethane, dried over Na_2SO_4 and concentrated. After work-up, the mixture was separated by flash chromatography to give the products.
13. *General glycosidation procedure for trichloroacetimidate donors*: To a solution of the diol (0.16 mmol) and the glycosyl donor(s) (0.16 mmol) in anhydrous CH_2Cl_2 (3 mL) were added molecular sieves 5 Å (1 mg/mg donor) and $BF_3{\cdot}OEt_2$ (0.048 mmol) at −78°C. The reaction was quenched after 15 min with saturated aqueous sodium bicarbonate, extracted with dichloromethane, dried over Na_2SO_4 and concentrated. The mixture was purified by flash chromatography to give the products.
14. *General glycosidation procedure for n-pentenyl donors*: To a solution of the diol (0.16 mmol) and the glycosyl donor(s) (0.16 mmol) in anhydrous CH_2Cl_2 (3 mL) were added molecular sieves 5 Å (1 mg/mg donor) and *N*-iodosuccinimide (3 equiv./donor) at −30°C. After stirring the mixture for 5 min, $BF_3{\cdot}OEt_2$ (0.048 mmol) was added. The mixture was allowed to warm to 0°C. After 40 min, the reaction was quenched and processed as described for *n*-pentenylorthoesters.
15. *Data for selected compounds*:
Compound **11b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56–7.01 (m, 25H, ArH), 5.54 (s, 1H, PhCH), 5.00 (d, $J=1.8$ Hz, 1H, H-1′), 4.92–4.44 (m, 9H), 4.30–3.43 (m, 12H), 3.30 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.05, 138.88, 138.48, 137.62, 132.11, 128.80, 128.26, 128.11, 127.83, 127.68, 127.48, 127.25, 126.36, 125.99, 102.25 (PhCH), 101.79 (C-1), 95.00 (C-1′), 79.65, 77.42, 75.08, 74.78, 74.67, 72.76, 72.50, 71.22, 70.33, 69.96, 69.34, 69.15, 67.32, 58.76, 55.31; API-ES positive: 828 $(M+Na)^+$; $\alpha_D=+49.5$ (*c* 0.5, $CHCl_3$).

Compound **12**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.57–7.18 (m, 25H, ArH), 5.63 (s, 1H, PhCH), 4.98 (d, $J=2.1$ Hz, 1H, H-1′), 4.92–4.50 (m, 9H), 4.33 (dd, $J=10.1$ Hz, 4.8 Hz, 1H), 4.12 (dd, $J=10.1$, 4.9 Hz, 1H), 3.98–3.69 (m, 10H), 3.29 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.41, 138.31, 138.11, 137.42, 129.06, 128.37, 128.24, 128.07, 127.79, 127.48, 126.27, 102.25 (PhCH), 100.35 (C-1), 99.51 (C-1′), 79.41, 76.76, 76.68, 75.50, 75.12, 73.39, 72.93, 72.68, 72.46, 69.57, 69.25, 67.68, 58.07, 55.50; API-ES positive: 828 $(M+Na)^+$; $\alpha_D=+42.5$ (*c* 3, $CHCl_3$).

Compound **11a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10–7.18 (m, 25H, ArH), 6.12 (t, $J=10.1$ Hz, 1H, H-4′), 5.93 (dd, $J=10.1$, 3.3 Hz, 1H, H-3′), 5.73 (dd, $J=3.2$, 1.8 Hz, 1H, H-2′), 5.65 (s, 1H, PhCH), 5.25 (d, $J=1.6$ Hz, 1H, H-1′), 4.79 (dt, $J=10.1$, 2.6 Hz, 1H), 4.70 (s, 1H, H-1), 4.55–4.28 (m, 4H), 4.11 (dd, $J=9.5$, 3.2 Hz, 1H), 3.98 (dd, $J=12.5$, 3.2 Hz, 1H), 3.84 (t, $J=10.2$ Hz, 1H), 3.51 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.13 (OC(O)Ph), 165.52 (OC(O)Ph), 165.35 (×2) (OC(O)Ph), 137.65, 133.36, 133.32, 133.03, 132.87, 130.01, 129.76, 129.70, 129.35, 129.26, 129.11, 128.52, 128.35, 128.25, 128.21, 126.14, 102.28 (PhCH), 101.79 (C-1), 95.63 (C-1′), 74.82, 73.09, 70.63, 70.32, 69.33, 68.58, 68.39, 66.46, 62.01, 58.78, 55.51; API-ES positive: 883 $(M+Na)^+$; $\alpha_D=+44.8$ (*c* 2, $CHCl_3$).

Compound **13**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16–7.84 (m, 8H), 7.63–7.18 (m, 37H), 6.16 (t, 1H, $J=10.2$ Hz), 5.92 (dd, 1H, $J=10.2$, 3.2 Hz), 5.74 (dd, 1H, $J=3.2$, 1.8 Hz), 5.66 (s, 1H), 5.17 (d, 1H, $J=1.8$ Hz), 4.88 (d, 1H, $J=1.8$ Hz), 4.86 (d, 1H, $J=10.8$ Hz), 4.85 (s, 1H), 4.79–4.63 (m, 5H), 4.52 (d, 1H, $J=10.5$ Hz), 4.50 (d, 1H, $J=12.0$ Hz), 4.46–4.36 (m, H), 4.09 (m, 1H), 4.02–3.71 (m, 10H), 3.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.06, 165.32, 165.29, 165.26, 138.42, 138.26, 138.22, 138.05, 137.68, 133.30, 132.98, 135.85, 130.08, 129.82, 129.75, 129.70, 129.41, 129.28, 129.13, 128.50, 128.37, 128.23, 128.10, 127.83, 127.76, 127.71, 127.65, 127.43, 126.11, 102.17, 99.88, 99.31, 95.70, 79.52, 75.56, 75.17, 75.12, 74.88, 73.33, 73.05, 72.69, 72.41, 71.39, 70.35, 70.33, 69.35, 69.10, 68.58, 66.42, 61.80, 58.20, 55.41; API-ES positive: 1401 $(M+NH_4)^+$; $\alpha_D=+39.5$ (*c* 1, $CHCl_3$). Anal. calcd for $C_{82}H_{78}O_{20}$: C, 71.19, H, 5.68. Found: C, 71.27, H, 5.73%.