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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 6564–6568

Propargyl 1,2-orthoesters as glycosyl donors: stereoselective synthesis of 1,2-*trans* glycosides and disaccharides

Gopalsamy Sureshkumar and Srinivas Hotha*

Division of Organic Chemistry: Synthesis, National Chemical Laboratory, Pune 411 008, India

Received 16 May 2007; revised 28 June 2007; accepted 5 July 2007

Abstract—Propargyl 1,2-orthoesters are identified as glycosyl donors. Various glycosides and disaccharides were synthesized in a stereoselective manner using $AuBr_3$ as the promoter. $AuBr_3$ may activate the alkyne resulting in the formation of a 1,2-dioxolenium ion and also behaves as a Lewis acid to facilitate the attack of the glycosyl acceptor. The versatility of the protocol was demonstrated using a panel of aglycones comprising aliphatic, alicyclic, steroidal and sugar alcohols.

Oligosaccharides and glycoconjugates are well known to play key roles in various biologically important processes.[1] Nature synthesizes glycans stereoselectively and the chemical synthesis of oligosaccharides[2] in such a manner is still a formidable task in spite of several elegant established approaches signifying scope for novel glycosyl donor development.[3] The 1,2-*trans* glycosidic bond has been achieved stereoselectively by employing the neighbouring group participation of a chiral auxiliary[4a,b] or often through a 2-*O*-acyl group **1** (Fig. 1).[2,4c] Alternatively, 1,2-*trans* glycosidation can also be accomplished with the intermediacy of a 1,2-dioxolenium ion **2**, which can be envisaged as being available from 1,2-orthoesters.[5] Orthoesters (or masked esters) are stable to bases but in the presence of mild acids, undergo stereoelectronic rearrangement.[5a,6]

However, in the absence of an aglycone, 1,2-orthoesters undergo acid-catalyzed rearrangement to give the corresponding glycosides due to the transfer of an alkoxy group to the anomeric centre.[7] One of the orthoester-based glycosyl donors **3** exploits activation of pent-4-enyl group using halonium ions and a Lewis acid.[5a–c]

Recent observations from our laboratory led to a novel $AuCl_3$ mediated transglycosylation protocol from per-*O*-benzylated propargyl glycosides to access a mixture of 1,2-*trans* **4** and 1,2-*cis* **5** glycosides (Fig. 1).[8a] Our efforts

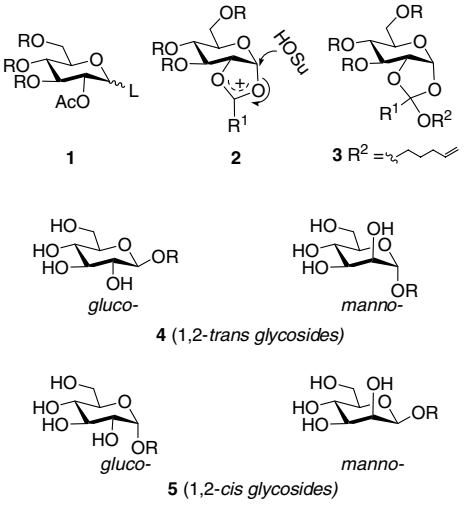

Figure 1. Structures of intermediates, and 1,2-*trans* and 1,2-*cis* glycosides.

to carry out the transglycosylation reaction in a stereoselective manner to obtain 1,2-*trans* glycosides utilizing a 2-*O*-acyl group proved futile. In continuation of this work, the search for a stereoselective 1,2-*trans* glycosylation by activation of propargyl groups[8a,9] prompted us to investigate propargyl orthoesters as possible glycosyl donors due to the alkynophilicity of gold reagents and their characteristic Lewis acidity.[9m] Accordingly, as part of our research programme[8] directed towards the development of protocols for novel glycoconjugate syntheses,

* Corresponding author. Tel.: +91 20 2590 2401; fax: +91 20 2590 2624; e-mail: s.hotha@ncl.res.in

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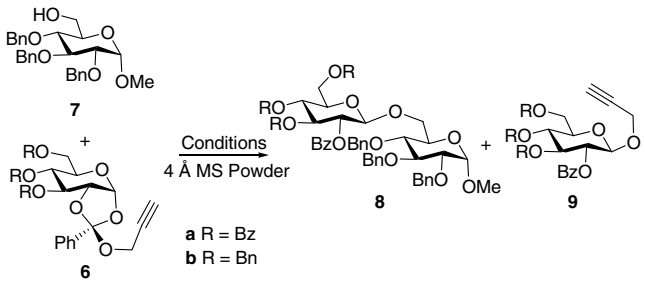
doi:10.1016/j.tetlet.2007.07.015



Entry	Conditions	Time (h)	%**8a**	%**9a**
1	$AuCl_3$ (5 mol%)/CH_3CN/60 °C	36	0	0
2	$AuCl_3$ (10 mol%)/CH_2Cl_2/25 °C	24	30	50
3	AuCl (10 mol%)/CH_2Cl_2/25 °C	36	0	0
4	Au_2O_3 (10 mol%)/CH_2Cl_2/60 °C	72	0	0
5	$HAuCl_4$ (10 mol%)/CH_2Cl_2/25 °C	1	45	28
6	$AuBr_3$ (10 mol%)/CH_2Cl_2/25 °C	5	63	20

Scheme 1. Propargyl 1,2-orthoesters as glycosyl donors.

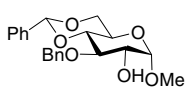
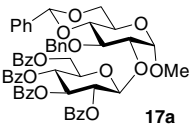
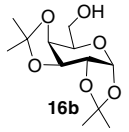
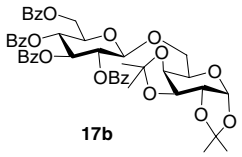
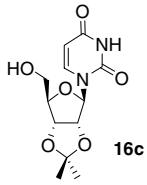
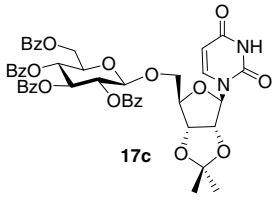
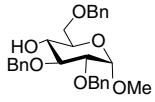
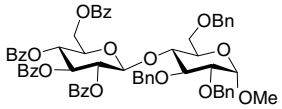
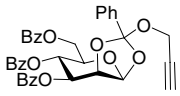
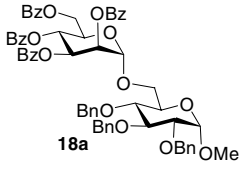
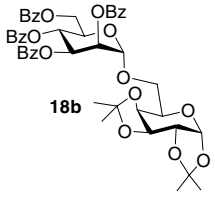
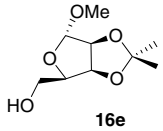
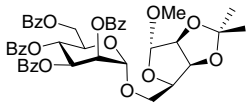
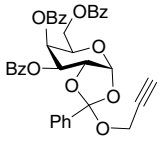
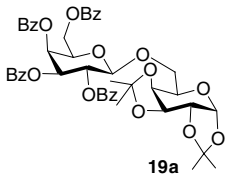
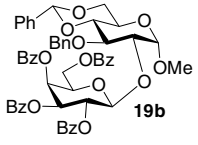
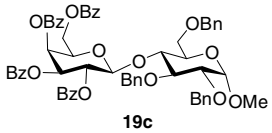
we explored the utility of propargyl orthoesters for the 1,2-*trans* stereoselective synthesis of glycosides and disaccharides.

To commence our investigation, propargyl orthoester **6a** was conveniently prepared[10] from tetra-*O*-benzoyl glucosyl bromide[11] using propargyl alcohol and 2,6-lutidine. Next, propargyl orthoester **6a** and aglycone **7** were subjected to $AuCl_3$ catalyzed glycosylation in CH_3CN at 60 °C (Scheme 1). The glycosyl donor **6a** was resistant to these reaction conditions, but switching the solvent to CH_2Cl_2 led to the formation of disaccharide **8a** (30%) and per-*O*-benzoylated propargyl β-glucoside **9a** (entries 1 and 2).[12] Efforts to promote the transformation with AuCl and Au_2O_3 were unsuccessful whereas $HAuCl_4$ catalyzed the glycosylation to give 45% of **8a** and 28% of **9a** (entries 3–5). Gratifyingly, 10 mol % of $AuBr_3$ in CH_2Cl_2 in the presence of 4 Å powdered molecular sieves under argon at room temperature for 5 h delivered the 1,2-*trans* disaccharide in

Table 1. Propargyl 1,2-orthoesters as glycosyl donors for glycoside synthesis

Entry	Glycosyl donor	Aglycone	Product	Time (h)	Yield (%)
1	**6a**	**10a**	**11a**	8	81
2	**6a**	**10b**	**11b**	2	74
3	**6a**	**10c**	**11c**	1	60
4	**12**	**10c**	**13a**	24	60
5	**12**	**10d**	**13b**	0.5	75
6	**14**	**10c**	**15a**	1	63
7	**14**	**10d**	**15b**	0.5	72

Table 2. Propargyl 1,2-orthoesters as glycosyl donors for disaccharide syntheses

Entry	Glycosyl donor	Aglycone	Product	Time (h)	Yield (%)
1	**6a**	 **16a**	 **17a**	10	42
2	**6a**	 **16b**	 **17b**	0.5	80
3	**6a**	 **16c**	 **17c**	2	50
4	**6a**	 **16d**	 **17d**	8	45
5	 **12**	**7**	 **18a**	24	70
6	**12**	**16b**	 **18b**	6	68
7	**12**	 **16e**	 **18c**	2	77
8	 **14**	**16b**	 **19a**	1	70
9	**14**	**16a**	 **19b**	10	45
10	**14**	**16d**	 **19c**	24	52

satisfactory yield (entry 6).[12,13] It is significant that the glycosylation of **6a** and **7** did not proceed in the presence of organic bases and the addition of freshly activated 4 Å powdered molecular sieves was essential for minimizing the formation of the per-*O*-benzoylated lactol.

The glycosylation reaction performed between donor **6b** and aglycone **7** resulted in the isolation of per-*O*-benzylated disaccharide **8b** in 58% yield.[12] The scope of this novel glycosylation method was explored in the perspective of glycoside and disaccharide syntheses.

Initially, we explored the utility of propargyl orthoesters for glycoside synthesis. As is evident from Table 1, the $AuBr_3$ promoted glycosylation reaction between glucosyl donor **6a** and various aglycones comprising aliphatic **10a**, alicyclic **10b** and steroidal **10c** gave the respective glucosides **11a**–**c** in a 1,2-*trans* stereoselective manner.[12] We extended the scope of this method to mannosyl **12** and galactosyl **14** 1,2-orthoesters[11] resulting in the formation of glycosides **13a** and **15a** in good yields.[12] Interestingly, glycosyl donors **12** and **14** reacted with 4-penten-1-ol to give the corresponding 4-pent-1-enyl glycosides **13b** and **15b**, which in turn can behave as glycosyl donors.[5]

The utility of 1,2-orthoester **6a** was gauged in the perspective of disaccharide formation using various sugar-based aglycones comprising primary alcohols (**7**, **16b**), secondary alcohols (**16a**, **16d**) and a nucleoside-based primary alcohol (**16c**). Gratifyingly, 1,2-orthoesters behaved as glycosyl donors in all the reactions giving the corresponding disaccharides in good yields.[12] It is pertinent to mention that the current glycosylation strategy was extended to mannosyl **12** and galactosyl **14** 1,2-orthoesters to obtain disaccharides **18a**–**c** and **19a**–**c**, respectively. The glycosylation reaction between a 1,2-orthoester-based glycosyl donor and carbohydrate derived secondary alcohols resulted in lower yields (Table 2, entries 1, 4 and 10) presumably due to the steric environment of the aglycone. It is important to mention that acid sensitive isopropylidene and benzylidene groups remained intact during the $AuBr_3$ mediated glycosylation reaction. In addition, we successfully carried out the glycosylation between donor **6a** and nucleoside **16c** to give disaccharide **17c**.[12]

Though a thorough mechanistic investigation is pending, it was envisioned that $AuBr_3$ might activate the propargyl moiety[8a] leading to the formation of a 1,2-dioxolenium ion **2** and also acted as a Lewis acid[9m] to promote the aglycone attack affording 1,2-*trans* glycosides in a stereoselective fashion.

In summary, we have developed a new O-glycosylation method that enables the synthesis of 1,2-*trans* glycosides from propargyl 1,2-orthoesters stereoselectively. We have demonstrated the scope and utility of propargyl 1,2-orthoesters as glycosyl donors in the syntheses of glycosides and disaccharides. Propargyl orthoesters gave access to 4-pentenyl glycosides, which can in turn behave as glycosyl donors.

Acknowledgements

S.H. thanks the DST, New Delhi (SR/S1/OC-06/2004) and DAE-BRNS-Young Scientist Research Award for financial support. S.H. is grateful for the encouragement of Dr. M. K. Gurjar and Dr. K. N. Ganesh. G.S.K. acknowledges a fellowship from CSIR-New Delhi.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.015.

References and notes

1. (a) Rudd, P. M.; Elliott, T.; Cresswell, P.; Wilson, I. A.; Dwek, R. A. *Science* **2001**, *291*, 2370–2376; (b) McAuliffe, J. C.; Hindsgaul, O. *Front. Mol. Biol.* **2000**, *30*, 249–285; (c) Varki, A. *Glycobiology* **1993**, *3*, 97–130; (d) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683–720; (e) Roy, R. In *Carbohydrate Chemistry*; Boons, G. J., Ed.; Chapman and Hall: UK, 1998; pp 243–321; (f) Kiessling, L. L.; Pohl, N. L. *Chem. Biol.* **1996**, *3*, 71–77; (g) Bovin, N. J.; Gabius, H.-J. *Chem. Soc. Rev.* **1995**, *24*, 413–421; (h) Gordon, E. J.; Sanders, W. J.; Kiessling, L. L. *Nature* **1998**, *392*, 30–31.
2. (a) Koeller, K. M.; Wong, C.-H. *Chem. Rev.* **2000**, *100*, 4465–4494; (b) Ragupathi, G.; Koide, F.; Livingston, P. O.; Cho, Y. S.; Endo, A.; Wan, Q.; Spassova, M. K.; Keding, S. J.; Allen, J.; Ouerfelli, O.; Wilson, R. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 2715–2725; (c) Plante, O. J.; Palmacci, E. R.; Seeberger, P. H. *Adv. Carbohydr. Chem. Biochem.* **2003**, *58*, 35–44; (d) Nguyen, H. M.; Chen, Y.; Duron, S. G.; Gin, D. Y. *J. Am. Chem. Soc.* **2001**, *123*, 8766–8772.
3. (a) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503–1531; (b) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212–235; (c) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155–173; (d) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21–123; (e) Shimizu, M.; Togo, H.; Yokoyama, M. *Synthesis* **1998**, 799–822; (f) Kahne, D.; Walker, S.; Cheng, Y.; van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881–6882; (g) Danishefsky, S. J.; Biolodeau, M. T. *Angew. Chem., Int. Ed.* **1996**, *35*, 1380–1419; (h) Witczak, Z. J.; Czernecki, S. *Adv. Carbohydr. Chem. Biochem.* **1998**, *53*, 143–199; (i) Hashimoto, S.; Honda, T.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1989**, 685–687; (j) Zhang, Z. Y.; Wong, C.-H. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinaÿ, P., Eds.; Wiley-VCH: Weinheim, 2000; Vol. 1, pp 117–134; (k) Mootoo, D. R.; Date, V.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 2662–2663; (l) Garegg, P. J. *Adv. Carbohydr. Chem. Biochem.* **1997**, *52*, 179–205; (m) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015–9020; (n) Demchenko, A. V.; Pornsuriyasak, P.; Meo, C. D.; Malysheva, N. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 3069–3072; (o) Kim, J. H.; Yang, H.; Boons, G.-J. *Angew. Chem., Int. Ed.* **2005**, *44*, 947–949; (p) Kim, K. S.; Kim, J. H.; Lee, Y. J.; Lee, Y. J.; Park, J. *J. Am. Chem. Soc.* **2001**, *123*, 8477–8481.
4. (a) Kim, J.-H.; Yang, H.; Boons, G.-J. *Angew. Chem., Int. Ed.* **2005**, *44*, 947–949; (b) Kim, J.-H.; Yang, H.; Park, J.; Boons, G.-J. *J. Am. Chem. Soc.* **2005**, *127*, 12090–12097; (c) Boons, G.-J. *Contemp. Org. Synth.* **1996**, *3*, 173–200.

5. (a) Roberts, C.; Madsen, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1995**, *117*, 1546–1553; (b) Allen, J. G.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1999**, *121*, 468–469; (c) Jayaprakash, K. N.; Radhakrishnan, K. V.; Fraser-Reid, B. *Tetrahedron Lett.* **2002**, *43*, 6953–6955; (d) Fraser-Reid, B.; Grimme, S.; Piacenza, M.; Mach, M.; Schlueter, U. *Chem. Eur. J.* **2003**, *9*, 4687–4692; (e) Bamhaoud, T.; Sanchez, S.; Prandi, J. *J. Chem. Soc., Chem. Commun.* **2000**, 659–660; (f) Radhakrishnan, K. V.; Sajisha, V. S.; Chacko, Jessy Maria *Synlett* **2005**, 997–999.
6. (a) King, J. F.; Allbutt, A. D. *Can. J. Chem.* **1970**, *48*, 1754–1769; (b) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: New York, 1983, Chapter 3.
7. Bochkov, A. F.; Zaikov, G. E. *Chemistry of the O-Glycosidic Bond*; Pergamon Press: Oxford, U.K., 1979, Chapter 2, 5–79.
8. (a) Hotha, S.; Kashyap, S. *J. Am. Chem. Soc.* **2006**, *128*, 9620–9621; (b) Hotha, S.; Kashyap, S. *J. Org. Chem.* **2006**, *71*, 364–367, and 852; (c) Hotha, S.; Kashyap, S. *Tetrahedron Lett.* **2006**, *47*, 2021–2023; (d) Maurya, S. K.; Hotha, S. *Tetrahedron Lett.* **2006**, *47*, 3307–3310; (e) Hotha, S.; Tripathi, A. *J. Comb. Chem.* **2005**, *7*, 968–976.
9. (a) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553–11554; (b) Hashmi, A. S. K.; Ding, L.; Bats, J. W.; Fischer, P.; Frey, W. *Chem. Eur. J.* **2003**, *9*, 4339–4345; (c) Asao, N.; Aikawa, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7458–7459; (d) Arcade, A.; Bianchi, G.; Marinelli, F. *Synthesis* **2004**, 610–618; (e) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164–11165; (f) Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 5350–5352; (g) Nieto-Oberhuber, C.; Munoz, M. P.; Bunuel, E.; Nevado, C.; Cardenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402–2406; (h) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962–6963; (i) Yao, X.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 6884–6885; (j) Shi, Z.; He, C. *J. Am. Chem. Soc.* **2004**, *126*, 5964–5965; (k) Shi, Z.; He, C. *J. Org. Chem.* **2004**, *69*, 3669–3671; (l) Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802–5803; (m) Hoffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387–391; (n) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333–346, and references cited therein.
10. (a) **6a** stereochemistry based on Ref. 5d; (b) Kochetkov, K.; Klimov, E. M.; Malysheva, N. N.; Demchenko, A. V. *Carbohydr. Res.* **1991**, *212*, 77–91; (c) Kochetkov, K.; Zhuin, V. M.; Klimov, E. M.; Malysheva, N. N.; Makarova, Z. G.; Ott, A. Y. *Carbohydr. Res.* **1987**, *164*, 241–254.
11. Mach, M.; Schlueter, U.; Mathew, F.; Fraser-Reid, B.; Hazen, K. C. *Tetrahedron* **2002**, *58*, 7345–7354.
12. All products were identified by ^{1}H, ^{13}C, DEPT NMR and CHNS analysis as well as mass spectrometry. See Supplementry data.
13. *Synthesis of glycosyl donor* **6a**: To a solution of 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (20.0 g, 0.0303 mol) in anhydrous CH_2Cl_2 (150 ml) was added 2,6-lutidine (15 ml), propargyl alcohol (9 ml, 0.1517 mol) and tetra-*n*-butylammonium iodide (50 mg) under argon at room temperature. Then, the reaction mixture was refluxed at 65 °C for 48 h, diluted with water and extracted with DCM (2 × 100 ml). The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo to yield a brownish-black residue which was purified by silica gel column chromatography using ethyl acetate–petroleum ether as the mobile phase to afford the glycosyl donor **6a** (16.34 g, 85%) as a white solid. *General experimental procedure for $AuBr_3$ mediated 1,2-trans stereoselective glycosylation*: To a solution of glycosyl donor (0.1 mmol), glycosyl acceptor (0.12 mmol) and 4 Å powdered molecular sieves in anhydrous CH_2Cl_2 (10 ml) was added $AuBr_3$ (10 mol %) under argon at room temperature. The reaction mixture was stirred at room temperature for the specified time and then filtered and the filtrate concentrated in vacuo. The resulting residue was purified by silica gel column chromatography using ethyl acetate–petroleum ether as the mobile phase.