A combined intramolecular–intermolecular one-pot glycosylation approach for the synthesis of a branched trisaccharide

Serafín Valverde,* Mercedes García, Ana M. Gómez and J. Cristóbal López

Instituto de Química Orgánica General (CSIC), Juan de la Cierva 3, 28006 Madrid, Spain. E-mail: iqov105@iqog.csic.es

Received (in Cambridge, UK) 24th January 2000, Accepted 29th March 2000 Published on the Web 20th April 2000

Intramolecular and intermolecular glycosidic couplings have been combined in a one-pot protocol for the synthesis of a branched trimannan.

In the last few years strategies for stereocontrol in saccharide synthesis^{1,2} based on intramolecular glycosidic couplings have been described,^{3–15} and the rapid assembly of oligosaccharides has been addressed through a new chemoselective glycosylation strategy, the one-pot glycosylation,16-20 which is based on reactivity differences between glycosyl donors.21-23 Our group⁸⁻¹⁰ has been interested in the development of an intramolecular approach for saccharide synthesis (e.g. $I \rightarrow II$, Scheme 1), in which medium rings^{8–15} rather than fivemembered intermediates³⁻⁷ are formed upon glycosidation. Here, we disclose some preliminary results of the extension of this approach for the synthesis of branched oligosaccharides by intermolecular glycosylation of an external glycosyl donor (e.g. III) onto the macrocyclic disaccharide (e.g. II \rightarrow IV, Scheme 1). More interestingly, the sequence $I \rightarrow IV$ has also been carried out in one-pot operations, and applied to the preparation of the biologically important methyl 3,6-di-O-(α-D-mannopyranosyl)- α -D-mannopyranose **9**²⁴ (Scheme 2).

Phenyl thioglycoside, 1, was readily transformed into the phthaloyl derivative 2, and its carboxylic acid function activated on treatment with $SOCl_2$ to furnish 3. Dialkylstannilen mediated coupling^{25,26} of acid chloride **3** with diol **4** gave mixed diester 5 which upon removal of the benzylidene ring led to triol 6. Glycosylation of 6 (CH₂Cl₂, NIS, TfOAg, 0 °C) led to disaccharide 7.† Intermolecular glycosylation of glycosyl donor 1 with 7 (CH₂Cl₂, NIS, TfOAg, -20 °C) proceeded regioselectively at O-3[‡] to give branched trimannose derivative 8§ (55% yield),¶ which upon deprotection and re-acetylation afforded methyl 3,6-di-O-(α-D-mannopyranosyl)-α-D-mannopyranose derivative, 9.§ A one-pot sequential glycosylation strategy was next examined in which cycloglycosylation of 6 $(CH_2Cl_2, TfOAg 0.3 \text{ equiv.}, 0.018 \text{ M}, -13 ^{\circ}C, 20 \text{ min})$ was followed by addition of **1** (1.1 equiv, -27 ^{\circ}C, 10 min) resulting in the formation of 8 (39% yield) [Scheme 3(a)]. Reaction of premixed 1 and 6 at lower temperature (CH₂Cl₂, TfOAg 0.3 equiv., 0.014 M, $-40 \degree \text{C}$, $40 \min$, then $-30 \degree \text{C}$, $40 \min$) resulted in the isolation of pseudotrisaccharide 10 (19%) along with unreacted 6 (30%) [(Scheme 3(b)], thus showing that inter-



Scheme 1

molecular glycosylation had taken place prior to the intramolecular coupling. On the hypothesis that the latter result could be a consequence of the difference in reactivities between donors **6** and **1**, owing to the influence of the electron withdrawing ester at *O*-6 in compound **6** when compared with the OTBDPS substituent at *O*-6 in **1**, as recently reported by Ley and coworkers in mannose systems,²² we decided to examine the one-pot glycosylation of **6** and **11**. Accordingly, treatment of compounds **6** and **11** with TfOAg (CH₂Cl₂, 0.03 M, TfOAg, -8 °C, 10 min) resulted in the formation of a mixture of saccharides from which the branched saccharide **12** (30% yield) was the major observed isomer [Scheme 3(b)].** The structure for trisaccharide **12** was assigned by correlation with compound **13**§ which had been prepared from trimannan **8** [Scheme 3(c)].

In our opinion, several aspects of the synthetic scheme deserve further comment: (i) tethered cyclo-glycosylation of triol **6** takes place with complete regio- and stereo-control at O-6 to afford disaccharide **7**; (ii) intermolecular glycosylation of donor **1** and diol **7** occurs regioselectively at O-3 to yield trisaccharide **8**. The regio- and stereo-selectivies in the glycosyl couplings observed in this work (i, ii) are similar to those reported by Kaur and Hindsgaul in their relevant synthesis of a related trimannan by classical non-tethered methods with minimal hydroxy group protection.²⁴



DOI: 10.1039/b0007710



Another interesting aspect of our results, with implications in the success of the synthetic scheme, is the striking difference in behavior between glycosyl donors 1 and 11, which is illustrated by the contrast between the results in Scheme 3(b) and 3(c). Thus, while one-pot glycosylation of 6 and 1 [Scheme 3(b)] resulted in the formation of pseudotrisaccharide 10 (with the intermolecular glycosylation taking place prior to the tethered cyclo-glycosylation), the one-pot glycosylation of 6 and 11 [Scheme 3(c)] yielded trisaccharide 12, as the major isomer formed,** where the cyclo-glycosylation had preceded the intermolecular glycosyl coupling. The tuning of donor reactivity, by changes in the protecting group at O-6, in mannopyranosyl donors, 1 and 11, is thus responsible for this behavior,²² and, in our opinion, when coupled to further tuning between intra- and inter-molecular glycosidic coupling could open a new avenue for the preparation of branched saccharides and small saccharide libraries.

The procedures outlined here, although not yet optimized, serve to illustrate a novel concept for one-pot glycosylation which relies in the kinetic acceleration of an intramolecular *versus* an intermolecular glycosidic coupling rather than in large disparities between the reactivities of different glycosyl donors. The optimization of this protocol by changes in the concentration and/or nature of the glycosyl donors is currently under study.

This research was supported with funds from the Dirección General de Enseñanza Superior (grants: PB96-0822 and PB97-1244). M. G. thanks the Ministerio de Educación y Cultura for a predoctoral scholarship.

Notes and references

 \dagger A minor amount of the corresponding $\alpha\text{-}1,3$ derivative was also isolated 3–5%.

‡ When the reaction was carried out at 0 °C in the presence of 1.7 equiv. of glycosyl donor 1, a tetrasaccharide resulting from the glycosylation of 1 at positions O-3 and O-4 in 8 was the only isolated compound (68%).

§ Selected data: for 8: $[\alpha]_{\rm D} = -5.7$ (c 0.5, CHCl₃); for 9: $[\alpha]_{\rm D} = +17.6$ (c 1, CHCl₃), API-ES positive (M⁺Na⁺): m/z 961.2; for 13: $[\alpha]_{\rm D} = -35.5$ (c 0.9, CHCl₃), API-ES positive (M⁺Na⁺): m/z 1007.5.

¶ Hydrolysis of the anomeric thiophenyl group was also observed.

|| Other attempts to carry out the one-pot glycosylation with premixed 1 and 6 (*e.g.* CH_2Cl_2 , TfOAg 0.3 equiv., 0.03 M, -13 °C, 20 min) gave complex reaction mixtures.

** Three other saccharides (10-15%) were also present in the reaction mixture, possibly resulting from the glycosidic coupling of **11** with hydrolyzed **6**.

- H. Paulsen, Angew. Chem., Int. Ed. Engl., 1990, 29, 823; H. Kunz, Angew. Chem., Int. Ed. Eng., 1987, 26, 294.
- 2 Reviews: K. Toshima and K. Tatsuta, *Chem. Rev.*, 1993, **93**, 1503; G.-J. Boons, *Tetrahedron*, 1996, **52**, 1095; S. J. Danishefsky and M. T. Bilodeau, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1380.
- 3 F. Barresi and O. Hindsgaul, J. Am. Chem. Soc., 1991, 113, 9376; F. Barresi and O. Hindsgaul, Can. J. Chem., 1994, 72, 1447.
- 4 G. Kim and G. Stork, J. Am. Chem. Soc., 1992, 114, 1087.
- 5 M. Bols, J. Chem. Soc., Chem. Commun., 1992, 913; M. Bols, Acta Chem. Scand., 1996, 50, 931.
- 6 Y. Ito and T. Ogawa, Angew. Chem., Int. Ed. Engl., 1994, 33, 1765; Y. Ito and T. Ogawa, J. Am. Chem. Soc., 1997, 119, 5562.
- 7 C. Krog-Jensen and S. Oscarson, J. Org. Chem., 1998, 63, 1780.
- 8 S. Valverde, A. M. Gómez, A. Hernández, B. Herradón and J. C. López, J. Chem. Soc., Chem. Commun., 1995, 2005.
- 9 S. Valverde, A. M. Gómez, J. C. López and B. Herradón, *Tetrahedron Lett.*, 1996, 37, 1105.
- 10 S. Valverde, M. García, A. M. Gómez and J. C. López, Synlett, 2000, 22.
- 11 T. Ziegler and R. Lau, *Tetrahedron Lett.*, 1995, 36, 1417; G. Lemanski and T. Ziegler, *Tetrahedron*, 2000, 56, 563.
- 12 H. Yamada, K. Imamura and T. Takahashi, *Tetrahedron Lett.*, 1997, 38, 391.
- 13 M. Müller, U. Huchel, A. Geyer and R. R. Schmidt, J. Org. Chem., 1999, 64, 6190.
- 14 R. J. Tennant-Eyles, B. G. Davis and A. J. Fairbanks, *Chem. Commun.*, 1999, 1037
- 15 M. Wakao, K. Fukase and S. Kusumoto, Synlett , 1999, 1911.
- 16 S. Raghavan and D. Kahne, J. Am. Chem. Soc., 1993, 115, 1580.
- 17 H. Yamada, T. Harada and T. Takahashi, J. Am. Chem. Soc., 1994, 116, 7919; H. Yamada, T. Harada, H. Miyazaki and T. Takahashi, *Tetrahedron Lett.*, 1994, 35, 3979; H. Yamada, T. Kato and T. Takahashi, *Tetrahedron Lett.*, 1999, 40, 1581.
- 18 H. K. Chenault and A. Castro, Tetrahedron Lett., 1994, 35, 9145.
- S. V. Ley and H. W. M. Priepke, Angew. Chem., Int. Ed. Engl., 1994, 33, 2292; P. Grice, S. V. Ley, J. Pietruszka, H. W. M. Priepke and E. P. E. Walther, Synlett, 1995, 781; P. Grice, S. V. Ley, J. Pietruszka, H. M. I. Osborn, H. W. M. Priepke and S. L. Warriner, Chem. Eur. J., 1997, 3, 431; M.-K. Cheung, N. L. Douglas, B. Hinzen, S. V. Ley and X. Pannecoucke, Synlett, 1997, 257; L. Green, B. Hinzen, S. J. Ince, P. Langer, S. V. Ley and S. L. Warriner, Synlett, 1998, 440.
- 20 G.-J. Boons and T. Zhu, Synlett, 1997, 809.
- 21 D. R. Mootoo, P. Konradsson and B. Fraser-Reid, J. Am. Chem. Soc., 1988, **110**, 5583; B. Fraser-Reid, Z. Wu, C. W. Andrews, E. Skowronski and J. P. Bowen, J. Am. Chem. Soc., 1991, **113**, 1434; B. Fraser-Reid, U. E. Udodong, Z. Wu, H. Ottosson, J. R. Merritt, C. S. Rao and C. Roberts, Synlett, 1992, 927.
- 22 N. L. Douglas, S. V. Ley, U. Lücking and S. L. Warriner, J. Chem. Soc., Perkin Trans. 1, 1998, 51.
- 23 Z Zhang, I. R. Ollmann, X.-S. Ye, R. Wischnat, T. Baasov and C.-H. Wong, J. Am. Chem. Soc., 1999, **121**, 734.
- 24 K. J. Kaur and O. Hindsgaul, *Glycoconjugate J.*, 1991, **8**, 90; K. J. Kaur, G. Alton and O. Hindsgaul, *Carbohydr. Res.*, 1991, **210**, 145.
- 25 S. David and S. Hanessian, *Tetrahedron*, 1985, **41**, 643; T. B. Grindley, in *Synthetic Oligosaccharides: Indispensable Probes for the Life Sciences*, ed. P. Kovac, ACS, Washington DC, 1994, ch. 4, p. 51.
- 26 A. Morcuende, S. Valverde and B. Herradón, *Synlett*, 1994, 89; B. Herradón, A. Morcuende and S. Valverde, *Synlett*, 1995, 455.