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Combinatorial synthesis of trisaccharides via solution-phase one-pot glycosylation

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Abstract

A library of 72 trisaccharides constructed from a combination of glucosides, galactosides, and mannosides via solution-phase one-pot glycosylation was synthesized rapidly using a manual synthesizer.

Keywords: glycosylation.

The combinatorial synthesis of oligosaccharides is a recent focus of our efforts in order to elucidate structure–activity relationships and to explore new bioactive molecules.[1,2] Recently, several approaches for the synthesis of oligosaccharide libraries not only via solution-phase but also via solid-phase have been reported.[3–13] We also reported that a one-pot, two step glycosylation is a potential method to rapidly assemble oligosaccharides.[14–16] This simple method should prove beneficial for the synthesis of a library of oligosaccharides because the ordinal steps required for the elongation of glycosides, i.e., deprotection and purification of each synthetic intermediate, are omitted.[17–19] Since we found that our reported DNA-cleaving enediyne molecules **I**–**III** containing mono-saccharides cleave DNA with certain sequence selectivity, such as 5′-C*G*G, 5′-C*A*G, and 5′-C*G*C, a variety of oligosaccharide-enediyne analogues **IV** should facilitate further studies in this area.[20,21] Herein we wish to report the synthesis of a trisaccharide-library consisting of a combination of glucosides, galactosides, and mannosides by solution-phase one-pot glycosylation.

In our previous reports, a one-pot, two-step glycosylation was accomplished using a combination of different leaving groups, i.e., bromide (-Br) and phenylthio group (-SPh), with selective activators, AgOTf and NIS–TfOH, respectively, leading to linear- and branched-trisaccharides (Scheme 1).[15,16] A library synthesis of linear-trisaccharides was examined through the combination of bromo glycosides **1**–**3**, phenylthio glycosides **4a**–**6a**, and 2-bromoethyl glycosides **7a**–**9a** or **7b**–**9b** (Fig. 1). The 2-bromoethyl group in **7**–**9** can be linked with the masked enediyne molecule to provide **IV** as previously

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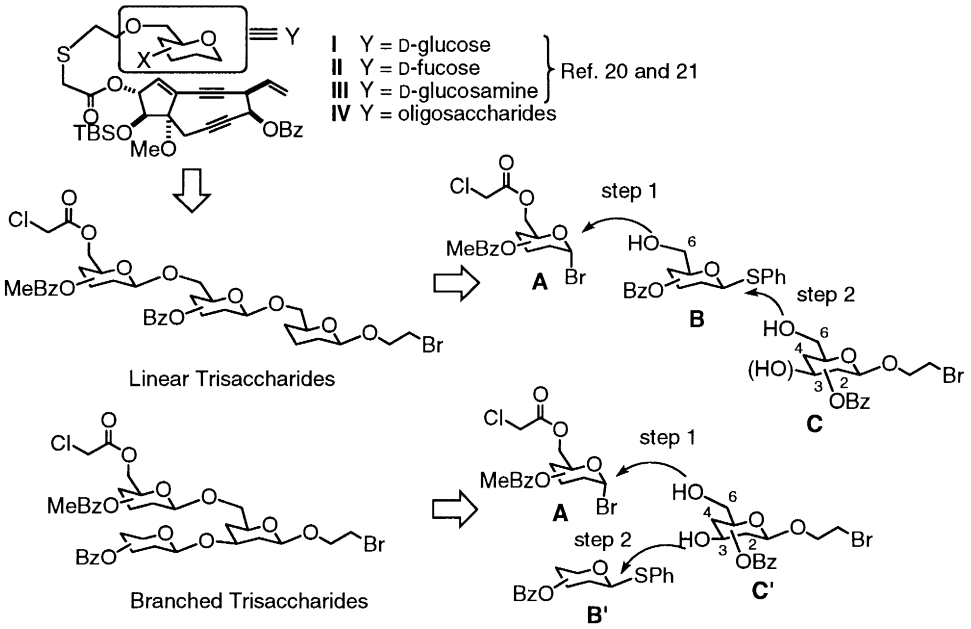

Scheme 1. Strategy for a library synthesis of trisaccharides by a one-pot glycosylation

reported.[20] A chloroacetyl group can be utilized for the polymer-supported synthesis of a library of the masked enediyne molecules containing a variety of oligosaccharides for the next stage. In the synthesis of the linear trisaccharides, nine reactions were carried out simultaneously: bromo glucoside **1** was placed in nine Teflon tubes on a Quest 210™ manual synthesizer.† Phenylthio glucoside **4a** was added to the first three vessels, phenylthio galactoside **5a** was added to the next three vessels, and

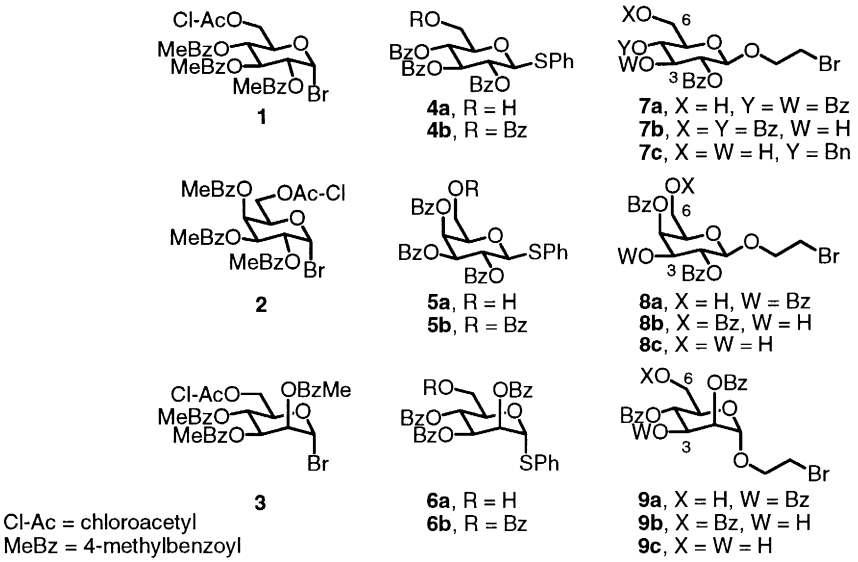

Fig. 1.

† A Quest 210 was purchased from Argonaut Technologies, USA.

phenylthio mannoside **6a** was added to the last three vessels. The mixtures were independently treated ($AgOTf/CH_2Cl_2/0°C$) in the presence of molecular sieves 4 Å. After all the reactions were complete as judged by TLC, 2-bromoethyl glycosides **7a**–**9a** or **7b**–**9b** were added to all three reaction vessels, respectively, as the combination of three components should be unique in all reaction vessels. Treatment of the reaction mixtures (NIS/cat. TfOH/0°C) provided the respective trisaccharides **10a**–**18a** or **10b**–**18b** in 64–99% yields after standard work-up and column chromatography. The results for all of the possible combinations for 54 trisaccharides are shown in Table 1. As anchoring is effected by the 2-position of the glycosyl donors, the anomeric linkages formed in the glycosylation were β-oriented (>95%) determined by the chemical shifts of ^{13}C NMR (98.4–102.3 ppm), except that α-formation was observed when the mannosides were used as glycosyl donors (95.9–98.0 ppm).[22]

Table 1
A library of linear 54 trisaccharides synthesized by one-pot glycosylation[a,b]

-Br	-SPh	-O(CH$_2$)$_2$Br	Product (Yield)[c]	-Br	-SPh	-O(CH$_2$)$_2$Br	Product (Yield)[c]
1	**4a**	**7a** or **7b**	**10a** (83) **10b** (74)	**2**	**6a**	**7a** or **7b**	**25a** (77) **25b** (79)
		8a or **8b**	**11a** (64) **11b** (99)			**8a** or **8b**	**26a** (78) **26b** (86)
		9a or **9b**	**12a** (89) **12b** (83)			**9a** or **9b**	**27a** (90) **27b** (63)
	5a	**7a** or **7b**	**13a** (91) **13b** (79)	**3**	**4a**	**7a** or **7b**	**28a** (79) **28b** (77)
		8a or **8b**	**14a** (73) **14b** (73)			**8a** or **8b**	**29a** (74) **29b** (78)
		9a or **9b**	**15a** (79) **15b** (91)			**9a** or **9b**	**30a** (91) **30b** (97)
	6a	**7a** or **7b**	**16a** (77) **16b** (97)		**5a**	**7a** or **7b**	**31a** (99) **31b** (99)
		8a or **8b**	**17a** (73) **17b** (90)			**8a** or **8b**	**32a** (86) **32b** (93)
		9a or **9b**	**18a** (82) **18b** (99)			**9a** or **9b**	**33a** (92) **33b** (99)
2	**4a**	**7a** or **7b**	**19a** (85) **19b** (99)		**6a**	**7a** or **7b**	**34a** (86) **34b** (99)
		8a or **8b**	**20a** (64) **20b** (95)			**8a** or **8b**	**35a** (75) **35b** (73)
		9a or **9b**	**21a** (78) **21b** (82)			**9a** or **9b**	**36a** (82) **36b** (77)
	5a	**7a** or **7b**	**22a** (98) **22b** (97)				
		8a or **8b**	**23a** (75) **23b** (99)				
		9a or **9b**	**24a** (87) **24b** (84)				

[a] **1-3** (1.10 equiv.) and **4a-6a** (1.05 equiv.) were used for **7a-9a** (1.00 equiv.). [b] **1-3** (1.05 equiv.) **4a-6a** (1.00 equiv.) were used for **7b-9b** (1.00 equiv.). [c] Yields were calculated based on 2-bromoethyl glycosides **7-9**.

The one-pot glycosylation was also utilized in the synthesis of branched trisaccharides as follows: Glycosyl bromide **1**–**3** and phenylthio glycosides **4b**–**6b** were employed as glycosyl donors and 3,6-diol **7c**–**9c** were used as glycosyl acceptors (Fig. 1). The mixtures of a different combination of **1**–**3**, **4b**–**6b**, and 3,6-diol **7c**, placed in nine Teflon tubes on a Quest 210, were treated with AgOTf (step 1 in Scheme 1), followed by NIS/TfOH (step 2 in Scheme 1). By repeating this process, the desired 18 branched trisaccharides **37**–**54** were isolated in good yields (72–99%) after standard work-up and column chromatography (Table 2). When the galactoside **8c** was used as a glycosyl acceptor, the one-pot reactions failed because both of the hydroxy groups of **8c** had reacted with glycosyl bromides **1**–**3** in the first step.

We have demonstrated that a synthesis of a library of 72 trisaccharides with a combination of glycosides, galactosides, and mannosides can be accomplished by a one-pot, two step glycosylation, which proved to be a powerful method for the rapid synthesis of a library of trisaccharides using a manual

Table 2
A library of branched 18 trisaccharides synthesized by one-pot glycosylation[a]

-Br	-SPh	-O(CH$_2$)$_2$Br	Product (Yield)[b]	-Br	-SPh	-O(CH$_2$)$_2$Br	Product (Yield)[b]
1	**4b**	**7c**	**37** (93)	**1**	**4b**	**9c**	**46** (95)
	5b	**7c**	**38** (93)		**5b**	**9c**	**47** (73)
	6b	**7c**	**39** (78)		**6b**	**9c**	**48** (72)
2	**4b**	**7c**	**40** (97)	**2**	**4b**	**9c**	**49** (99)
	5b	**7c**	**41** (84)		**5b**	**9c**	**50** (74)
	6b	**7c**	**42** (99)		**6b**	**9c**	**51** (87)
3	**4b**	**7c**	**43** (99)	**3**	**4b**	**9c**	**52** (99)
	5b	**7c**	**44** (89)		**5b**	**9c**	**53** (89)
	6b	**7c**	**45** (99)		**6b**	**9c**	**54** (99)
1-3	**4b-6b**	**8c**	- (0)[c]				

[a] **1-3** (1.05 equiv.) and **4b-6b** (1.50 equiv.) were used for **7c-9c** (1.00 equiv.). [b] Yields were calculated based on 2-bromoethyl glycosides **7c-9c**. [c] Both hydroxy groups of 3,6-diol **8c** reacted with glycosyl bromides **1-3**.

synthesizer. Further study of library syntheses having other linkages, i.e., at the 2- and 4-positions of **C**, and the 2,6-, 4,6-, 2,3-, 2,4-, and 3,4-positions of **C′** instead of the 3,6-position (Scheme 1) is now underway in our laboratory.

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