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Glycosidation via conjugate addition of anomeric alkoxides to nitroalkenes and nitrosoalkenes

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Abstract—The conjugate addition reactions of protected pyranose alkoxides to both nitroalkenes and nitrosoalkenes, as a route to 2-nitroalkyl, 2-oximinoalkyl and 2-oxoalkyl glycosides, are described.

Despite the myriad methods for the formation of *O*-glycosides available today,[1] there remains a need for the development of novel strategies allowing access to glycoside linkages within certain structural templates. As part of a total synthesis program towards the antibiotic lactonamycin **1**[2] (Fig. 1), we required a reliable method for (L)-α-rhodinosylation. Since we considered the direct glycosylation[3] of a sterically hindered α-hydroxy-ketone would be problematic, we decided to explore a non-traditional method[4] for the construction of the glycosidic bond.

The potent reactivity of both nitroalkenes and nitrosoalkenes as conjugate addition acceptors, coupled with the facile conversion of the nitro or nitroso group into other functionalities, such as ketones,[5] nitriles[6] and amines,[7] has prompted the extensive use of conjugate addition reactions of diverse nucleophiles to such Michael acceptors.[8] A number of examples exist for the conjugate addition of oxygen nucleophiles to nitroalkenes and nitrosoalkenes,[8,9] however, to date the use of anomeric alkoxides in the formation of 2-nitroalkyl glycosides remains unexplored. Lubineau et al.[10] have reported the addition of the sodium salt of 3,4,6-tri-*O*-acetyl-2-acetamido-2-deoxy-β-D-glucose to 3-(4-toluenesulfonyl-oxy)propenal to provide the corresponding vinyl glycoside via an addition–elimination sequence. In addition, Dixon and coworkers have reported the synthesis of 1,2-amino alcohols using the diastereoselective Michael addition of δ-lactols to (*E*)-nitroalkenes.[10] We proposed to harness the acceptor properties of nitro- and nitrosoalkenes to allow for the preparation of *O*-glycosides through the Michael addition of anomeric alkoxides. In this communication, we describe studies on the conjugate addition reactions of a range of pyranose derivatives to 1-nitrocyclohexene, 1-nitrosocyclohexene and related systems to produce the corresponding glycoside addition products.[11]

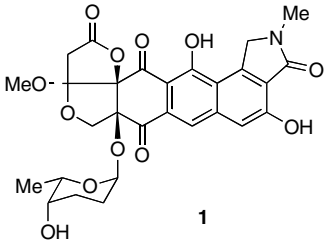

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Figure 1.

A range of anomeric alcohols **2**–**7** (Fig. 2) was prepared by the literature procedures.[12] The 2-deoxy-glucose derivative **8** was prepared in three steps from D-glucal following Danishefsky's method.[13] 4-*O*-^{t}Butyldimethylsilyloxy-L-rhodinopyranose **13** was synthesized using a modification of the previous synthesis of Schlessinger and Graves[14] with the replacement of toxic tin and chromium reagents (Scheme 1). Protection of methyl (*S*)-lactate **9** as its benzyl ether followed by DIBAl-H reduction afforded the corresponding aldehyde. This was allowed to react with allylmagnesium bromide under chelation control conditions[15] to afford the monoprotected diol

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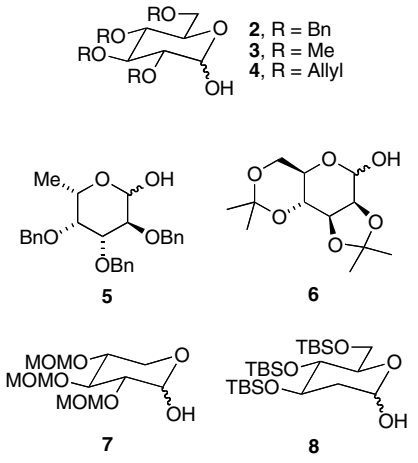
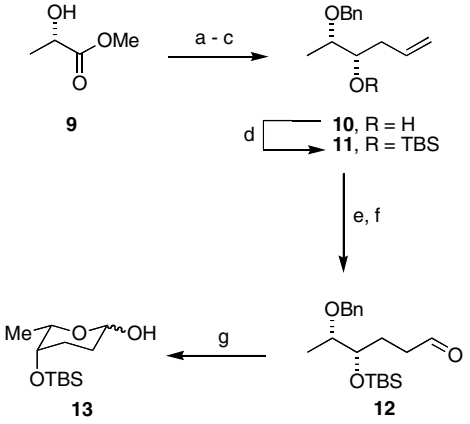


Figure 2.



Scheme 1. Reagents and conditions: (a) NaH, Bu_4NI (1 mol%), $PhCH_2Br$, THF, 85%; (b) DIBAl-H, CH_2Cl_2, −78 °C; (c) allylmagnesium bromide, $MgBr_2{\cdot}Et_2O$, CH_2Cl_2, −78 °C; (d) $^tBuMe_2SiCl$, imidazole, DMAP (5 mol%), DMF, 89% over three steps; (e) cyclohexene, $BH_3{\cdot}SMe_2$, THF; NaOH, H_2O_2, 50 °C, 81%; (f) Dess–Martin periodinane, CH_2Cl_2, 89%; (g) H_2 (3 atm), 10% Pd/C, EtOH, 81%.

10 with excellent diastereoselectivity (>95%). Silylation gave alkene **11**,which was subjected to hydroboration with subsequent Dess–Martin oxidation[16] to reveal aldehyde **12**. Debenzylation under hydrogenolysis conditions afforded the desired (L)-rhodinose derivative **13** in 44% overall yield from methyl (*S*)-lactate **9**.

Deprotonation of alcohol **2** using *n*-butyllithium at −10 °C followed by the addition of 1-nitrocyclohexene **24** and quenching with acetic acid at −78 °C gave the corresponding glycoside **14** (56%) as a mixture of anomers and 2-nitrocyclohexyl diastereoisomers. Further chromatography and ^1H–^1H and NOE NMR studies allowed for the identification of the stereochemical bias of the reaction. The product **14** was obtained predominantly as the α-anomers (**14a** and **14b**)[17] with a selectivity of 4:1 [(**14a** and **14b**):(**14c** and **14d**)] (Fig. 3). In addition the 2-nitrocyclohexyl residue was formed predominantly as the *cis*-isomer, although there was no

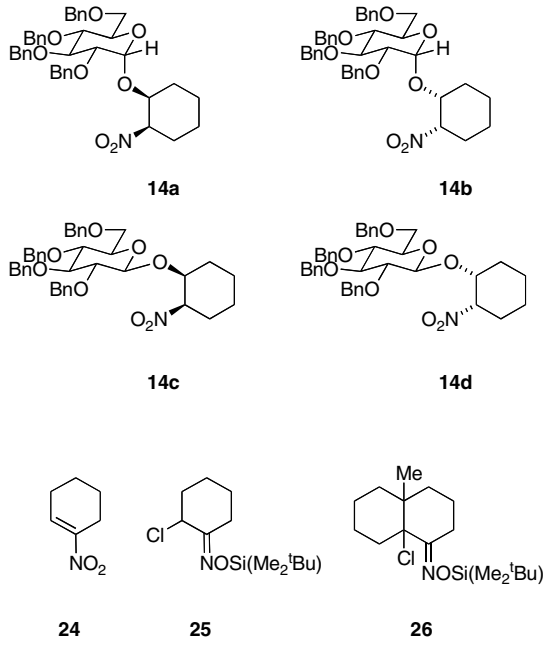
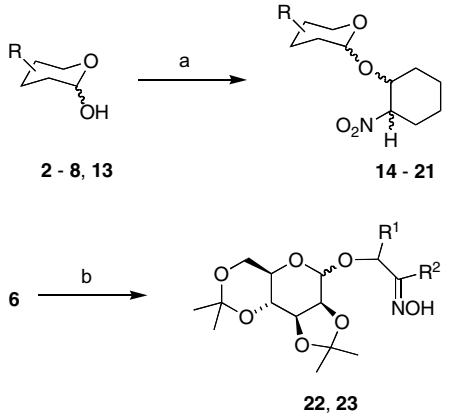


Figure 3.

significant absolute stereochemical bias in the nitrocyclohexyl unit.

The procedure[18] was extended to the preparation of the 2-nitrocyclohexyl glycosides **15**–**21**, which were obtained in good yields as mixtures of isomers (Scheme 2, Table 1). The reaction conditions were sufficiently mild and tolerated a range of protecting groups on the glycosyl donor. It is clear from entries 1–3 and 7 that glucopyranose derivatives with methyl and silyl ether protecting groups underwent glycosidation in higher yields than related benzyl and allyl ethers. Alongside the glucose derivatives investigated, the study showed that fucose **5** (entry 4), mannose **6** (5), xylose **7** (6) and rhodinose **13** (8) derivatives were also successfully coupled. Of particular importance, with respect to the lactonamycin program, was the effective glycosylation of the 2-deoxy sugars **8** and **13** (entries 7 and 8).



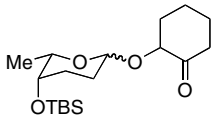
Scheme 2. Reagents and conditions: (a) *n*-BuLi, THF, −10 °C; **24**, 25 °C; AcOH, −78 °C (Ref. 18); (b) **25** or **26**, *n*-BuLi, THF, −10 °C; Bu_4NF, −78 °C; NH_4Cl, H_2O (Ref. 20).

Table 1. Synthesis of 2-nitroalkyl and 2-oximinoalkyl glycosides

Entry	Pyranose	Reagent[a]	Product (%)	α:β Ratio
1	**2**	**24**	**14** (56)	4:1
2	**3**	**24**	**15** (65)	—[b]
3	**4**	**24**	**16** (44)	—[b]
4	**5**	**24**	**17** (51)	3:1
5	**6**	**24**	**18** (48)	—[b]
6	**7**	**24**	**19** (52)	—[b]
7	**8**	**24**	**20** (63)	—[b]
8	**13**	**24**	**21** (55)	3:1
9	**6**	**25**	**22** (69)	—[b]
10	**6**	**26**	**23** (62)	—[b]

[a] Glycosidation using nitrocyclohexene **24**, or nitrosoalkenes generated in situ from the oximes **25** or **26**.
[b] Ratios not determined.

The 2-nitrocyclohexyl glycosidations were extended to related reactions using the labile nitrosoalkenes derived from the α-chloro-ketoximes **25** and **26**, by desilylation and chloride elimination in situ (Table 1, Scheme 2). The required oximes **25** and **26** were, respectively, prepared from the corresponding α-chloro-ketones and *O*-(*t*-butyldimethylsilyl)hydroxylamine.[19] Sequential addition of *n*-butyllithium (at −10 °C) and tetrabutylammonium fluoride in THF to pyranose **6** and oxime **25** gave the corresponding glycoside **22** (69%) as a mixture of isomers. In the same way,[20] pyranose **6** and oxime **26** were converted into the glycoside **23** (62%), also as a mixture of isomers



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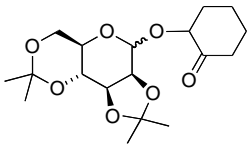

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Finally, a representative 2-nitroalkyl glycoside **21** was converted into the corresponding 2-oxoalkyl glycoside **27** (50%, α:β 3:1) using an oxidative Nef reaction with potassium permanganate, potassium hydroxide and magnesium sulfate in methanol.[21] Secondly, the 2-oximinoalkyl glycoside **22** was converted into the corresponding 2-oxoalkyl glycoside **28** (71%) using manganese dioxide in hexane[5] and was obtained as a mixture of isomers. These oxidative conversions are relevant to the synthesis of the keto glycoside unit of lactonamycin **1**.

In conclusion we have developed novel glycosylation strategies for the preparation of 2-nitroalkyl, 2-oximinoalkyl and 2-oxoalkyl glycosides, through the conjugate addition of anomeric alkoxides to nitro- or nitrosoolefins. This methodology has been applied to a range of pyranose sugars affording the desired addition products in good yields and, in several cases, with promising levels of α-diastereoselectivity. Further work concerned with the formation of *O*-glycosides through the conjugate addition of anomeric alkoxides will be reported in due course.

Acknowledgements

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17. In all cases, the major relative configuration of the $CH(NO_2)CH(O$-glycoside) unit was determined to be *cis*. The absolute configuration was not determined.
18. General procedure: *n*-BuLi in hexanes (2.5 M; 0.4 mL, 1 mmol) was added dropwise with stirring to the pyranose (1 mmol) in THF (2 mL) at −10 °C under N_2. After 30 min, 1-nitrocyclohexene (32 mg, 0.25 mmol) was added, the mixture allowed to warm up to ambient temperature and stirred for further 16 h. After cooling to −78 °C, AcOH (0.25 mL) was added, the mixture allowed to warm up to room temperature and diluted with H_2O (10 mL). The mixture was extracted with Et_2O (3×10 mL) and the combined organic extracts washed with water (2×25 mL), dried ($MgSO_4$) and filtered. Rotary evaporation and chromatography (hexane–AcOEt) gave the desired glycoside product as a mixture of isomers.
19. α-Chlorocyclohexanone is commercially available. Oxime **26** was prepared as a mixture of isomers from 3,4,5,6,7,8-hexahydro-1(2*H*)naphthalenone by conjugate addition of $MeLi–CuBrSMe_2$ in Et_2O at −25 °C to provide (±)-4a-methyl-1-decalone (57%), chlorination using SO_2Cl_2 in CCl_4 and condensation with *O*-(*t*-butyldimethylsilyl)-hydroxyl-amine (17% over two steps). See: (a) House, H. O.; Thompson, H. W. *J. Org. Chem.* **1961**, *26*, 3729; (b) Yakura, T.; Tanaka, K.; Kitano, T.; Uenishi, J.; Ikedaa, M. *Tetrahedron* **2000**, *56*, 7715; (c) Boeckman, R. K., Jr.; Silver, S. M. *J. Org. Chem.* **1975**, *40*, 1755.
20. *n*-BuLi in hexane (2.5 M; 0.4 mL, 1.0 mmol) was added dropwise with stirring to **6** (260 mg, 1.0 mmol) and **25** (261 mg, 1.0 mmol) in anhydrous THF (2 mL) under N_2 at −10 °C. After 20 min, the mixture was cooled to −78 °C and Bu_4NF in THF (1 M, 1.2 mL, 1.2 mmol) added dropwise over 15 min. The mixture was allowed to slowly reach ambient temperature and, after 2 h, quenched with saturated aqueous NH_4Cl (10 mL). The mixture was extracted with Et_2O (2×25 mL) and the combined organic extracts washed with water and brine and dried ($MgSO_4$). Rotary evaporation and chromatography ($SiO_2CH_2Cl_2$–MeOH; 9:1) gave **22** (256 mg, 69%) as a mixture of isomers.
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