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6-*O*-Benzyl- and 6-*O*-Silyl-*N*-acetyl-2-amino-2-*N*,3-*O*-carbonyl-2-deoxyglucosides: Effective Glycosyl Acceptors in the Glucosamine 4-OH Series. Effect of Anomeric Stereochemistry on the Removal of the Oxazolidinone Group

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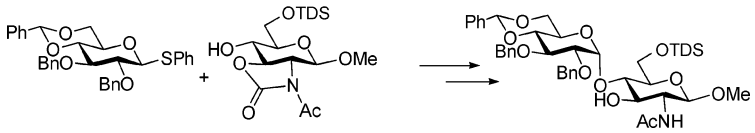

The 4-OH groups of both α- and β-methyl glycosides of *N*-acetylglucosamine, protected with an oxazolidinone spanning the nitrogen and O-3, and bearing benzyl or silyl protection on O-6, show excellent reactivity as acceptors in couplings to a range of glycosyl donors. The enhanced reactivity of these acceptors is attributed in part to the tied back nature of the oxazolidinone, which reduces hindrance around the nucleophilic oxygen. The *N*-acetyloxazolidinone function also reduces the tendency seen in simple *N*-acetylglucosamines toward amide glycosylation, and removes the possibility of problematic hydrogen bonding networks. In the β-, but not the α-, series selective hydrolysis of the *N*-acetyloxazolidinone directly to the *N*-acetylglucosamine was possible with barium hydroxide, a feature attributed to chelate formation between the acetamide carbonyl group and the glycosidic oxygen in the β-series.

Introduction

Hydroxyl groups on the 4-position of otherwise protected *N*-acetylglucosamine derivatives are widely acknowledged to be among the most difficult alcohols to glycosylate.[1] On the basis of variable-temperature NMR studies, we have suggested that the low reactivity of these alcohols arises from intermolecular hydrogen bonding of the amide group, which effectively increases steric bulk around the nucleophilic alcohol.[2] Such intermolecular effects should be magnified at lower temperatures and are, therefore, particularly relevant to many modern glycosylation reactions, many of which operate significantly below room temperature. A recent report on the efficient glycosylation of the 4-OH group of polymer-supported *N*-acetylglucosamine derivatives may be interpreted as lending support to the H-bonding hypothesis as the polymer obviously isolates the individual molecules, rendering intermolecular hydrogen bonding improbable.[3] In addition to structural effects, it has been demonstrated that the amide group in *N*-acetylglucosamine derivatives may itself be glycosylated by active species leading to *O*-glycosyl imidates.[4] Glycosylation of the acetamide group in this manner, which obviously depletes the pool of available glycosyl donor as well as increasing the steric hindrance in the immediate vicinity of the acetamide, may be one reason underlying the deleterious effect of even remote acetamido groups on some glycosylation reactions.[5] Yet another possible reason for the failure of many glycosylations of *N*-acetylglucosamine 4-OH acceptors, at least under the conditions of the sulfoxide method, is the formation of cyclic oxazines between the acceptor alcohol and the acetamide.[6] Despite the widespread acknowledgment of the *N*-acetylglucosamine acceptor reactivity problem, and the recent investigations into the specific causes, there are

(1) (a) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155. (b) Debenham, J.; Rodebaugh, R.; Fraser-Reid, B. *Liebigs Ann./Recl.* **1997**, 791.

(2) Crich, D.; Dudkin, V. *J. Am. Chem. Soc.* **2001**, *121*, 6819.

(3) Mogemark, M.; Elofsson, M.; Kihlberg, J. *J. Org. Chem.* **2003**, *68*, 7281.

(4) Liao, L.; Auzanneau, F.-I. *Org. Lett.* **2003**, *5*, 2607.

(5) Lucas, R.; Hamza, D.; Lubineau, A.; Bonnaffé, D. *Eur. J. Org. Chem.* **2004**, 2107.

(6) Aguilera, B.; Fernando-Mayoralas, A. *J. Org. Chem.* **1998**, *63*, 2719.

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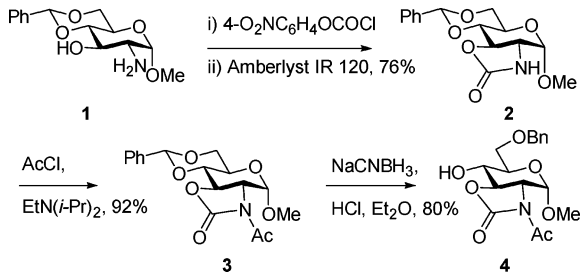
numerous reports[7] of successful couplings either to the 4-OH of *N*-acetylglucosamine acceptors themselves, or involving acceptors or donors with proximal or remote amides and carbamates. From these reports it is obvious that no single reason for the typical lack of reactivity holds under all sets of glycosylation conditions.[8] Whatever the reason, or combination of reasons, considerable effort has been devoted to overcoming this problem with most studies focusing on masking the amide group. Among a wide variety of amine protecting groups investigated in this context, the phthaloyl and azido systems are the most popular; with the latter being preferred in terms of reactivity of the 4-OH group as demonstrated, at least for the sulfoxide method, by a series of competition reactions.[2] A more recent paper has shown, also by means of competition reactions, that use of the *N*-trichloroethoxycarbonyl (NTroc) group affords greater glucosamine 4-OH reactivity than the comparable 2-deoxy-2-phthaloyl and 2-deoxy-2-azido donors in trichloroacetimidate couplings.[9] Tetrachlorophthaloyl[10] and sulfonamide[11] protected glucosamine 4-OH derivatives also appear to have considerable potential as acceptor alcohols. With the exception of the 2-azido-2-deoxy system, which is readily converted in a single step to the *N*-acetylglucosamine function with potassium thioacetate,[12] the various *N*-protected glucosamine 4-OH derivatives in common use all require two steps for transformation to the *N*-acetylglucosamine after the glycosylation reaction. With a view to streamlining synthetic protocols we have been interested in developing other surrogates for the *N*-acetylglucosamine that (i) avoid the manipulation of triflyl azide necessary for the preparation of the 2-azido-2-deoxyglucose system,[13] (ii) enhance the reactivity of the 4-OH group toward glycosylation, and (iii) are readily cleaved under mild conditions directly to the *N*-acetylglucosamine function itself in a single reaction step. Initially, we explored the *N*,*N*-diacetylglucosamine and *N*-acetyl-*N*-benzyl groups[2] but these failed to meet all of our criteria, and we therefore turned our attention to the *N*-acetyl-2-*N*,3-*O*-carbonyl functionality on which we now report in full.[14]

SCHEME 1. Preparation of the α-Configured Acceptor 4



Results and Discussion

We reasoned that an *N*-acetyloxazolidinone bridging N-2 and O-3 of glucosamine would (i) prevent hydrogen bonding by removing the amide NH from play, (ii) reduce steric hindrance around O-4, and (iii) be readily converted to the requisite acetamide in a single step after glycosylation. The presence in Nature of both α- and β-glycosidic linkages to the anomeric center of *N*-acetylglucosamine,[15] together with a series of intriguing reports on the differing nucleophilicity of pyranosidic alcohols dependent on their anomeric configuration,[16] prompted us to undertake the synthesis of both α- and β-methyl glycosides of the *N*-acetyloxazolidinone protected glycosyl acceptors. Synthesis of the α-anomer (**4**) began with the known 4,6-*O*-benzylidene protected glucosamine derivative **1**[17] and oxazolidinone formation by sequential treatment with *p*-nitrophenyl chloroformate and Amberlyst IR 120 resin (Scheme 1). Acetylation then gave the *N*-acetyloxazolidinone **3**, whose benzylidene group was successfully cleaved regioselectively in the standard manner to give the acceptor **4**.[18]

Interestingly, when the same reaction sequence was applied to the β-series (Scheme 2), beginning with the known amino alcohol **5**,[19] cleavage of the benzylidene acetal with sodium cyanoborohydride and HCl in ether led to the α-anomer **4** and not to the desired product. There are numerous successful examples of the reductive cleavage of benzylidene acetals to benzyl ethers using the cyanoborohydride/HCl in systems bearing β-glycosidic bonds[18] including contemporaneous ones from our own laboratories,[20] and therefore this anomerization was

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(8) Presumably, the issue of matching or mismatching of donors with particular acceptors, juxtaposed with the basic issue of reactivity, plays a role here. For discussions of matching and mismatching in glycoside bond formations see: (a) Paulsen, H. In *Selectivity, a Goal for Synthetic Efficiency*; Bartmann, W., Trost, B. M., Eds.; Verlag Chemie: Basel, Switzerland, 1984. (b) Spijker, N. M.; van Boeckel, C. A. A. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 180. (c) Fraser-Reid, B.; López, J. C.; Gómez, A. M.; Uriel, C. *Eur. J. Org. Chem.* **2004**, 1387.

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(14) For a preliminary communication on a part of this work see: Crich, D.; Vinod, A. U. *Org. Lett.* **2003**, *5*, 1297.

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(16) (a) Magaud, D.; Dolmazon, R.; Anker, D.; Doutheau, A.; Dory, Y. L.; Deslongchamps, P. *Org. Lett.* **2000**, *2*, 2275. (b) Zhu, X.-X.; Cai, M.-S.; Zhou, R.-L. *Carbohydr. Res.* **1997**, *303*, 261. (c) Rochepeau-Jobron, L.; Jacquinet, J.-C. *Carbohydr. Res.* **1998**, *305*, 181.

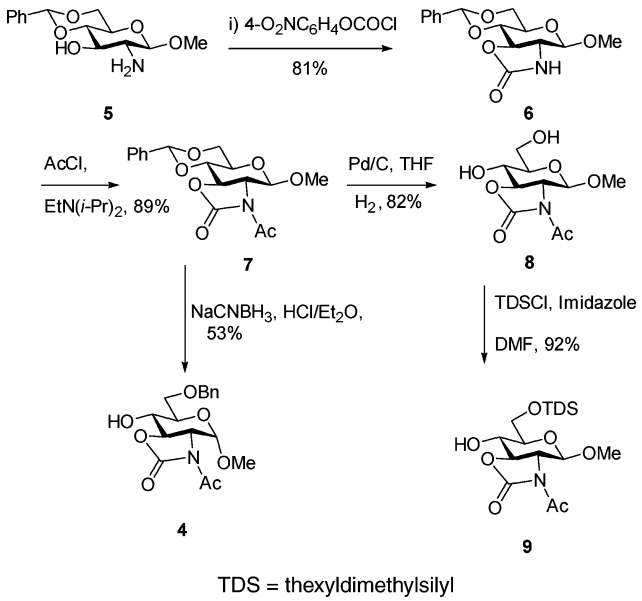
(17) Bauer, T.; Tarasiuk, J.; Pasiczek, K. *Tetrahedron*: *Asymmetry* **2002**, *13*, 77.

(18) (a) Garegg, P. J. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Dekker: New York, 1993; p 53. (b) Garegg, P. J.; Hultberg, H.; Wallin, S. *Carbohydr. Res.* **1982**, *108*, 97.

(19) Haller, M. F.; Boons, G. J. *Eur. J. Org. Chem.* **2002**, 2033.

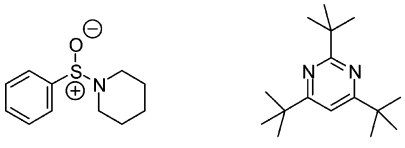
(20) Crich, D.; Banerjee, A.; Yao, Q. *J. Am. Chem. Soc.* **2004**, *126*, 14930.

SCHEME 2. Preparation of the β-Configured Acceptor 9



unexpected. Presumably, the reaction is assisted here by the strain imposed on the pyranose ring by the presence of the trans-fused oxazolidinone ring, which facilitates ring opening by cleavage of the C1−O5 bond. Repeated attempts at overcoming this epimerization by controlling the acidity of the medium were unsuccessful and consequently we turned to an alternative sequence. Thus, hydrogenolysis of the acetal gave the diol **8**, which underwent clean monosilylation on the primary alcohol with thexyldimethylsilyl chloride to afford the β-acceptor **9**.

With acceptors **4** and **9** in hand, a series of couplings were carried out with a range of thioglycosides with preactivation at −60 °C in dichloromethane, using the combination of 1-benzenesulfinylpiperidine (BSP) and trifluoromethanesulfonic anhydride[7j,21] in the presence of the hindered base 2,4,6-tri-*tert*-butylpyrimidine (TTBP).[22] As is evident from the results presented in Table 1, both acceptors performed well with all donors tested.



We attribute the good to excellent yields in each of these couplings to a combination of the absence of the NH bond, the reduced nucleophilicity of imides as compared to amides, which attenuates the problem of protecting group glycosylation, and the relatively unhindered nature of the acceptor alcohols due to the "tied back" oxazolidinone protecting group.[23] When a direct comparison was made between acceptors **4** and **9** both gave comparable yields and selectivities in all cases but two: both the 4,6-*O*-benzylidene protected mannosyl donor **10** (Table 2, entries 1 and 2) and the tetra-*O*-benzyl protected glucosyl donor **13** (Table 2, entries 3 and 4) exhibited a shift in favor of the α-anomeric product on going from acceptor **4** to acceptor **9**. In the case of mannosyl donor **10** this change is manifested in the reduced β-selectivty on coupling to **9** (Table 2, entries 1 and 2), whereas with the already α-selective glucosyl donor **13** the trend is reflected in increased α-selectivity (Table 2, entries 3 and 4). This pattern is potentially attributable to the change in steric environment arising from the difference in protecting groups at O-6 in the two acceptors and, thus, there would seem to be no reason to invoke a change in reactivity with anomeric configuration. Anomeric selectivities follow the established pattern for thioglycoside/BSP couplings,[7j,21] or the closely related sulfoxide method,[21,24] likely proceeding via the intermediate α-glycosyl triflate[7j,25] through a displacement that likely involves a transient contact ion pair.[26] Thus, 4,6-*O*-benzylidene protected mannosylation was β-selective (Table 1, entries 1 and 2),[7h,j] while glucosylation was somewhat α-selective with the tetrabenzyl donor (Table 1, entries 3 and 4) and even more so with the 4,6-*O*-benzylidene protected system (Table 1, entries 5 and 6).[7j,27] 4,6-*O*-Benzylidene protected galactosylation was completely α-selective (Table 1, entries 7 and 8),[28] as was rhamnosylation, with both a standard fully disarmed donor and a 2,3-*O*-carbonate protected donor (Table 1, entries 9 and 10),[29] and fucosylation with a perbenzylated donor (Table 1, entry 11).[24] The only system necessitating comment is the 4,6-*O*-benzylidene mannosylation (Table 1, entries 1 and 2), which, while β-selective as expected, was considerably less so than comparable couplings to other glucosamine 4-OH acceptor alcohols such as the 2-azido-2-deoxyglucose system,[2] the phthaloyl protected glucosamine,[2] and even the low-yielding but never-theless selective *N*-acetylglucosamine system itself;[7h] at the present time we have no satisfactory explanation for this deviation from high β-selectivity.

Among the myriad of other glycosylation methods available,[30] we have briefly surveyed the applicability of glycosyl acceptor **4** in Kahne's sulfoxide method (Scheme 3, Table 2, entry 2),[21,24] Gin's dehydrative coupling sequence (Scheme 3, Table 2, entry 3),[21,31] and Schmidt's trichloroacetimidate protocol (Scheme 3, Table 2, entry 4)l[32] and find that it performs well in all three.

Although the two anomers **4** and **9** behaved analogously in glycosylation reactions, a significant difference was observed in the deprotections of the two anomeric series of disaccharides. Thus, in the disaccharides derived from the α-methyl acceptor **4**, it proved impossible to selectively hydrolyze the oxazolidinone ring without

(21) Crich, D.; Lim, L. B. L. *Org. React.* **2004**, *64*, 115.
(22) Crich, D.; Smith, M.; Yao, Q.; Picione, J. *Synthesis* **2001**, 323.
(23) Inspection of coupling constants indicated the $^4C_1$ chair conformation to be retained in both the α- and β-methyl series, indicating that the reactivity is not due to an unusual conformation of the glucosamine pyranose ring.
(24) Yan, L.; Kahne, D. *J. Am. Chem. Soc.* **1996**, *118*, 9239.
(25) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217.
(26) Crich, D.; Chandrasekera, N. S. *Angew. Chem., Int. Ed.* **2004**, *40*, 5386.
(27) Crich, D.; Cai, W. *J. Org. Chem.* **1999**, *64*, 4926.
(28) Crich, D.; de la Mora, M.; Vinod, A. U. *J. Org. Chem.* **2003**, *68*, 8142.
(29) Crich, D.; Vinod, A. U.; Picione, J. *J. Org. Chem.* **2003**, *68*, 8453.
(30) Barresi, F.; Hindsgaul, O. *J. Carbohydr. Chem.* **1995**, *14*, 1043.
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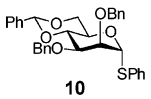
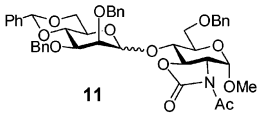
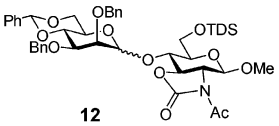
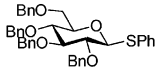
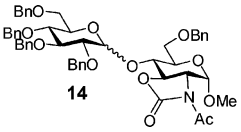
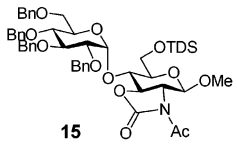
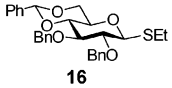
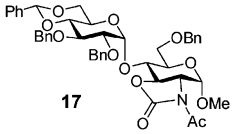
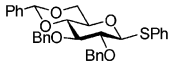
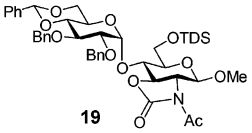
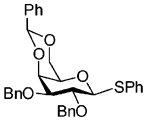
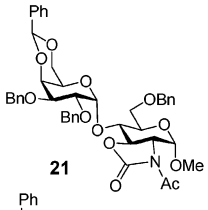
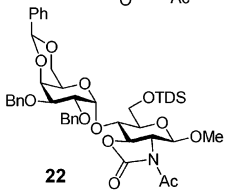
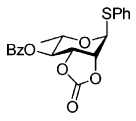
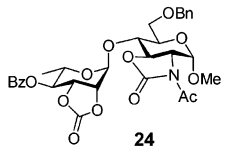
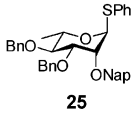
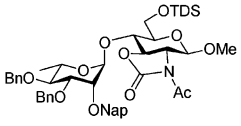
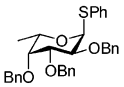
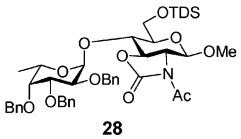
(32) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21.

TABLE 1. Glycosylation of Acceptors 4 and 9 by the Thioglycoside/BSP/Tf_2O Method

Entry	Donor	Acceptor	Coupled Product	Anomeric[a] Ratio (α/β)	% Yield[b]
1	**Mannose**  **10**	**4**	 **11**	1:2.7	82
2		**9**	 **12**	1:2.2	80
3	**Glucose**  **13**	**4**	 **14**	6.2:1	78
4		**9**	 **15**	α only	78
5	 **16**	**4**	 **17**	α only	87
6	 **18**	**9**	 **19**	α only	83
7	**Galactose**  **20**	**4**	 **21**	α only	85
8		**9**	 **22**	α only	73
9	**Rhamnose**  **23**	**4**	 **24**	α only	66
10	 **25**	**9**	 **26**	α only	77
11	**Fucose**  **27**	**9**	 **28**	α only	74

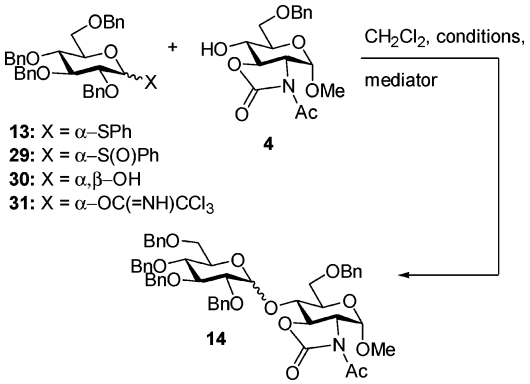
[a] Anomeric ratios were determined by integration of the ^1H NMR spectra of reaction mixtures. [b] Yields refer to pure isolated products.

TABLE 2. Alternative Methods for the Formation of 14 from 4

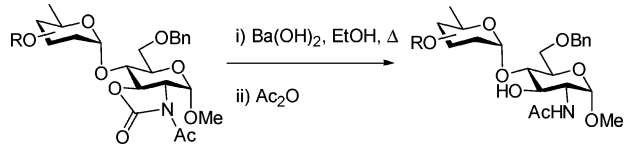
entry	donor	mediator, conditions	anomeric ratio[a] (α/β)	% yield[b]
1	**13**[c]	BSP, TTBP, Tf_2O, −60 °C	6.2:1	78
2	**29**	TTBP, Tf_2O, −60 °C	α only	63
3	**30**	Ph_2SO, Tf_2O, TTBP, −40 °C	α only	59
4	**31**	TMSOTf, −30 °C	3.5/1	82

[a] Anomeric ratios were determined by integration of the ^1H NMR spectra of reaction mixtures. [b] Yields refer to pure isolated products. [c] Entry 1 is reproduced here from Table 1 for convenient comparison.

SCHEME 3. Coupling to 4 by Alternative Methods



SCHEME 4. Removal of the Oxazolidinone in the α-Methyl Series

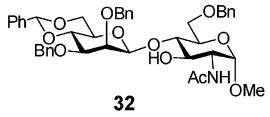
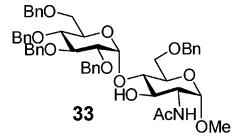
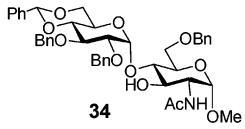
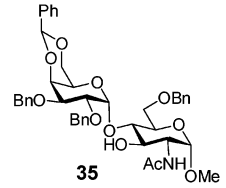
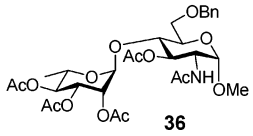


competing cleavage of the acetamide.[33] Accordingly, a protocol was developed involving treatment with barium hydroxide in hot ethanol,[34] followed by reacetylation of the crude reaction mixture with acetic anhydride to give the required *N*-acetylglucosamine based disaccharides (Scheme 4, Table 3).

Remarkably, in the β-series selective cleavage of the oxazolidinone ring was possible with aqueous ethanolic barium hydroxide, leading directly to the *N*-acetylglucosamine-based disaccharides, without the need for reacetylation, thereby fulfilling the last of our design criteria (Scheme 5, Table 4).[35]

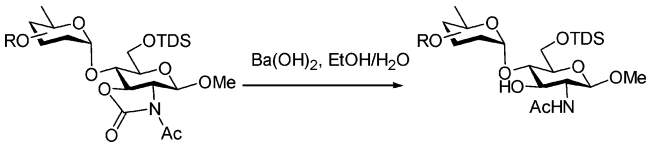
While it is clear from Schemes 1 and 2 and the anomerization observed on exposure of **7** to HCl in ether that the β-series are intrinsically less stable than the α-series, as might be expected on simple anomeric effect grounds, we believe that the root cause of the greater ease and selectivity of oxazolidinone cleavage in the

TABLE 3. Removal of the Oxazolidinone in the α-Methyl Series

Disaccharide	Deprotected product	% Yield[a]
11β	 **32**	80
14α	 **33**	62
17	 **34**	76
21	 **35**	81
24	 **36**	48[b]

[a] Yields refer to pure isolated products. [b] In this example the acetylation was conducted with acetic anhydride and pyridine.

SCHEME 5. Removal of the Oxazolidinone in the β-Methyl Series



β-series is unrelated. As is widely appreciated,[36] *N*-acyloxazolidinones enjoy two predominant conformations with the carbonyl dipoles aligned either syn- or antiperiplanar. In the absence of metal ions the antiperiplanar conformation is preferred whereas the syn-conformation is favored in the presence of Lewis acidic metals. In the α-series both the syn- and anti-conformations are possible as the glycosidic bond is roughly orthogonal to the plane of the *N*-acetyloxazolidinone system (Scheme 6). Presumably, hydrolysis in the presence of the barium cation involves the formation of a chelate with the syn-conformation in which both carbonyl groups are activated, hence the lack of selectivity.

In the β-series the equatorial glycosidic bond is in the approximate plane of the *N*-acetyloxazolidinone and destabilizes both the anti and syn conformations, owing to the presence of dipolar interactions and steric problems, respectively, leading to intrinsically higher reactivity. On addition of the coordinating metal the anti

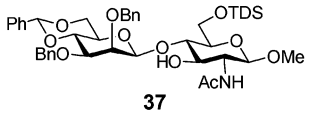
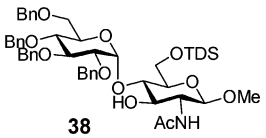
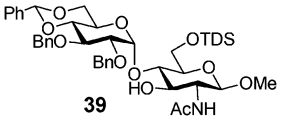
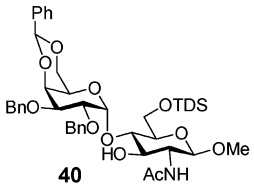
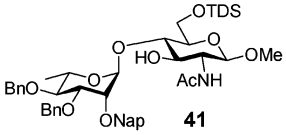
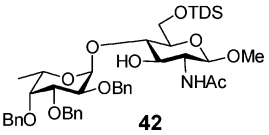
(33) This behavior is typical of *N*-acyl oxazolidinones. For example, see: (a) Shinzo, K.; Tsutomu, Y.; Shiroshi, S. *J. Org. Chem.* **1989**, *54*, 513. (b) Scholz, K. H.; Heine, H. G.; Hartmann, W. *Tetrahedron Lett.* **1978**, *19*, 1467. (c) Ning, X.; Ciufolini, M. A. *Tetrahedron Lett.* **1995**, *36*, 6595.

(34) Kang, S. H.; Choi, H.; Kim, J. S.; Youn, J.-H. *Chem. Commun.* **2000**, 227.

(35) Under these mild conditions, only very low yields of product were obtained from the α-series. For example, only 22% of **35** could be isolated from the complex reaction mixture obtained on exposure of disaccharide **21** to barium hydroxide.

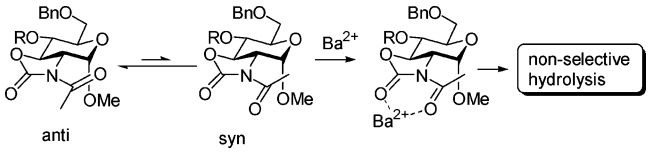
(36) (a) Evans, D. A.; Bartoli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (b) Ghosh, A. K.; Fidanze, S.; Senanayake, C. H. *Synthesis* **1998**, 937.

TABLE 4. Removal of the Oxazolidinone in the β-Methyl Series

Disaccharide	Deprotected product	% Yield[a]
12β	 **37**	69
15	 **38**	67
19	 **39**	79
22	 **40**	73
26	 **41**	79
28	 **42**	72

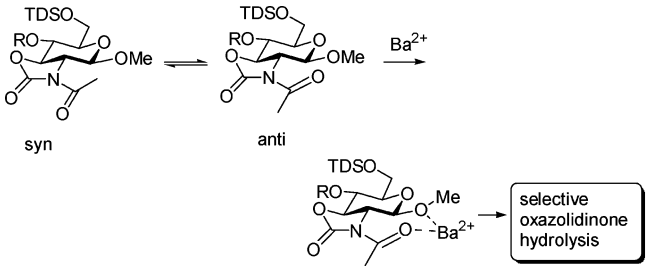
[a] Yields refer to pure isolated products.

SCHEME 6 *N*-Acetyl Oxazolidinone Conformations and Nonselective Cleavage in the α-Series



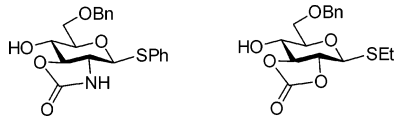
conformer will be stabilized by chelate formation involving the acetyl carbonyl and the glycosidic oxygen. Chelation involving the two carbonyl groups in the syn conformation, however, will not be favored as it does not alleviate the steric clash of the acetyl group with the equatorial glycosidic bond. The preferential chelation of the metal between the acetyl carbonyl group and the

SCHEME 7 *N*-Acetyl Oxazolidinone Conformations and Selective Cleavage in the β-Series



glycosidic oxygen will have the effect of transferring the amide resonance, normally shared by both carbonyls, mainly toward the acetyl group thereby activating the oxazolidinone toward hydrolysis (Scheme 7). After hydrolysis of the oxazolidinone ring the remaining acetamide is free to adopt the usual conformation of this group, in which the N−H bond is antiperiplanar to the axial C2−H bond, and the system is free of unfavorable interactions with the glycosidic bond.[37]

In work closely related to that presented here, it was reported that the oxazolidinone-protected thioglycoside **43** serves as a viable glycosyl acceptor in neighboring group-directed, β-selective couplings to several glycosyl donors.[38] However, glycosylation of the oxazolidinone N−H bond was an important competing reaction, underlining the importance of the *N*-acetyl group in acceptors **4** and **9**. It has also been demonstrated that the carbonate protected thioglycoside **44** is a viable acceptor in glycosylation reactions,[39] and it would seem reasonable at this stage to suggest that tied back, cyclic protecting groups for the 2,3-positions will likely generally increase the reactivity of the 4-OH as an acceptor alcohol in a broad range of situations.



43 **44**

Acknowledgment. We thank the NIH (GM 62160) for support of this work.

Supporting Information Available: Full experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0482559

(37) Fowler, P.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1996**, *79*, 269.
(38) Kerns, R. J.; Zha, C.; Benakli, K.; Liang, Y.-Z. *Tetrahedron Lett.* **2003**, *44*, 8069.
(39) Zhu, T.; Boons, G.-J. *Org. Lett.* **2001**, *3*, 4201.