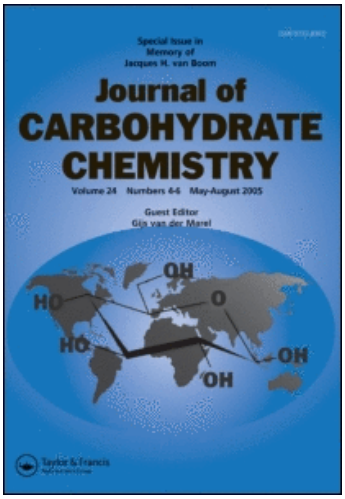

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Serine and Threonine Schiff Base Esters React with β-Anomeric Peracetates in the Presence of $BF_3{\cdot}Et_2O$ to Produce β-Glycosides

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Serine and Threonine Schiff Base Esters React with β-Anomeric Peracetates in the Presence of $BF_3 \cdot Et_2O$ to Produce β-Glycosides

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Improved procedures are reported for the glycosylation of L-serine and L-threonine utilizing activated Schiff base glycosyl acceptors, which are less expensive and more efficient alternatives to published methods. L-serine or L-threonine benzyl ester hydrochloride salts were reacted with the diarylketimine *bis*-(4-methoxyphenyl)-methanimine in CH_3CN at rt to form the more nucleophilic Schiff bases **3a** and **3b** in excellent yield. These Schiff bases exhibited ring-chain tautomerism in $CDCl_3$ as shown by ^1H NMR. Schiff bases **3a** and **3b**, acting as glycosyl acceptors, reacted at rt with simple sugar peracetate donors with $BF_3 \cdot OEt_2$ promotion to provide the corresponding L-serine and L-threonine O-linked glycosides in excellent yields and purities. The dipeptide ester Schiff base Ar_2C = N-Ser-Val-OCH_3 **3e** also reacted to provide β-glycosides in excellent yields, and without epimerization. With microwave irradiation the reactions were complete in 2 to 5 min. To investigate this reaction further, classical AgOTf-promoted Koenigs-Knorr reaction of D-glucopyranosyl, lactosyl, and maltosyl bromides were examined, providing the β-glycosides with yields ranging from 35% to 68%. The difference in reactivity between α- and β-carbohydrate peracetate donors was remarkable. The less configurationally stable D-xylopyranosyl tetra-acetate (a pentose) showed no selectivity ($\alpha vs \beta$-configuration) toward the Schiff bases.

Keywords Glycosylation; Glycoside; Schiff base; Serine; Glycopeptide; Lewis acid

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Introduction

Many well-documented glycosylation procedures, both old and new, exist for the synthesis of complex glycosides.[1] For example, in the Koenigs-Knorr[2] and Helferich[3] reactions, reactive glycosyl bromides and chlorides are reacted with alcohols or phenols in the presence of transition metal salts such as Ag(I) or Hg(II) in a suitable solvent. The AgOTf-catalyzed Koenigs-Knorr reaction (Hanessian modification) of glycosyl bromides used for preparation of β-O-glycosylated amino acids requires low temperatures accompanied by slow introduction of the promoter.[4] The α-product and ortho-ester are often formed in addition to the β-glycoside. The glycosyl bromides are easily hydrolyzed and many have short half-lives unless stored in very dry conditions in a freezer. Sugar fluorides have been exploited by Micheel,[5] Mukaiyama,[6] Nicolaou,[7] and others.[8] The glycosyl fluoride is a more stable glycosyl donor compared to the corresponding chlorides or bromides and can be activated in the presence of different Lewis acids. The more reactive iodides have also been used recently as glycosyl donors by Gervay.[9] The trichloroacetimidates, introduced by Schmidt[10] as glycosyl donors in 1980, are generally activated by catalytic amounts of a Lewis acid, with $Me_3SiOSO_2CF_3$ (TMSOTf) and $BF_3{\cdot}Et_2O$ being the most commonly used reagents. Numerous methodologies based on alkyl- and aryl-thioglycosides have also become useful building blocks in oligosaccharide synthesis.[11] Fugedi et al.[12] developed thiophilic activators such as dimethyl(methylthio)sulfonium triflate (DMTST) as mildly oxidative promoters. Kahne et al.[13] developed a two-step procedure based on sulfoxide intermediates as glycosyl donors activated with triflic anhydride. Fraser-Reid et al.[14] developed the 4-pentenyl glycosides that can be activated with Br_2 or similar oxidative reagents to produce intermediate bromosugar donors in situ that undergo further activation with Ag^+ or Hg^{++} salts.

As useful and diverse as the aforementioned methods may be, all of them require the synthesis of relatively complex donors, which is a disadvantage when preparing amino acid glycosides on large scale. Often instability (shelf life) of the donor is an issue. The use of easily prepared and stable sugar acetates as donors avoids these problems. Kilberg's coupling of sugar acetates with FMOC-protected amino *acids* (unprotected carboxyl groups) provided a direct pathway to glycosyl amino acids, albeit in modest yield.[15] In this method, $BF_3{\cdot}OEt_2$ or $SnCl_4$ activation of glycosyl acetates in CH_2Cl_2/CH_3CN at rt was demonstrated to be feasible. The major limitation with this method is that laborious purification procedures are required, which become increasingly tedious as the scale of the reaction is increased, and the yields are often low as a result. Very recently microwave-assisted glycosylation of FMOC-Ser-OBn using $FeCl_3$ in the presence of 4 Å molecular sieves in $PhCH_3$ or CH_3CN was reported to provide β-glycosides in short reaction times and moderate yields.[16] It was suggested that the α-forms of the sugar acetates investigated were less reactive due to the anomeric effect.

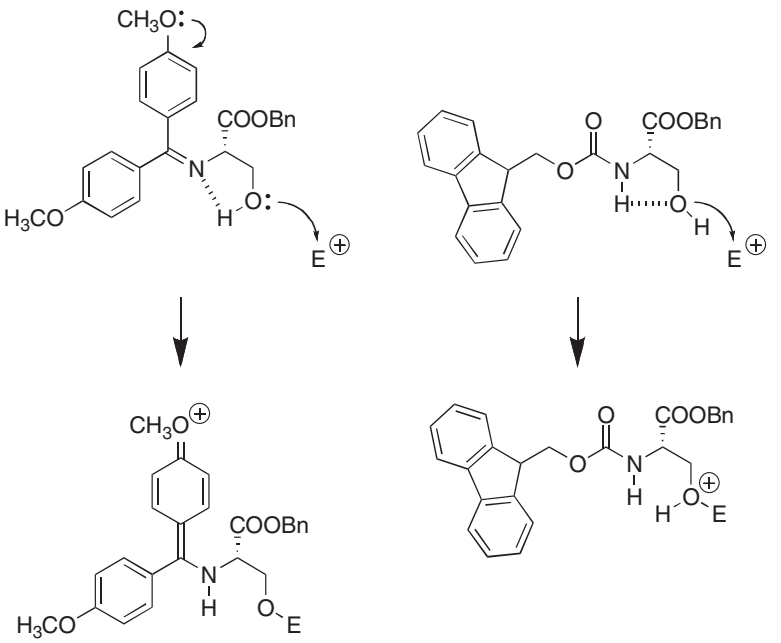


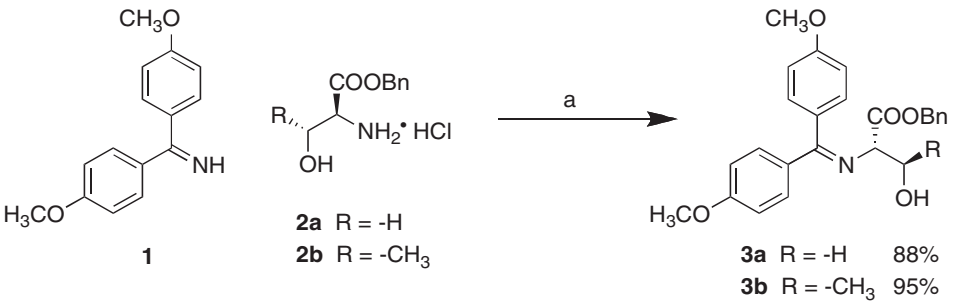
Figure 1: Protection of the amine (Schiff base vs. FMOC) can alter the H-bonding patterns and influence glycosyl acceptor properties of the serine derivatives. The Schiff base lone pair (:N=) can act as an internal base to enhance the basicity of the serine OH, whereas the Fmoc proton (H—N) can act as a proton donor to reduce the basicity of the serine OH.

The use of Schiff bases in glycosylation was reported by Szabó et al. in 1991 employing glycosyl bromides as donors in the presence of Ag(I) salts.[17] This chemistry was further extended to amino acid glycosides[18] for use in the synthesis of O-linked glycopeptides that penetrate the blood-brain barrier.[19] The x-ray crystal structure of the benzophenone Schiff base of methyl L-threonate determined by Wijayaratne et al.[20] confirmed the existence of the oxazolidine tautomer, at least in the solid state. The hypothesis is that the Schiff bases are more effective nucleophiles (Fig. 1) for glycosylation than FMOC-protected serine or threonine derivatives in the preparation of amino acid glycosides. In this study, we show that the tautomer population of the Schiff base depends on whether it is serine or threonine derived and also on the aromatic substituents.

RESULTS

Preparation of Serine and Threonine Schiff Bases

The ketimine, *bis*-(4-methoxyphenyl)methanimine (**1**), and serine (**2a**) or threonine (**2b**) benzyl ester hydrochloride salts (Sch. 1) were prepared using published methods (vide infra). The crystalline diarylketimine (**1**) was formed



Scheme 1: Preparation of Schiff bases **3a** and **3b**. Reagents and conditions: (a) CH_3CN, rt, overnight.

by reacting 1-bromo-4-methoxybenzene and Mg° shavings in THF under reflux to provide the aryl Grignard reagent, which was subsequently reacted with *p*-CH_3O-C_6H_4CN and quenching the reaction with anhydrous CH_3OH. This provided the product **1** in good yield, which crystallized directly from the reaction mixture.[21] The benzyl ester hydrochloride salts **2a** and **2b** were prepared from L-serine or L-threonine and $PhCH_2OH$ in the presence of *p*-toluenesulfonic acid. The L-serine/L-threonine benzyl ester *p*-toluenesulfonic salts formed from the reactions were not isolated, but were evaporated to an oil in vacuo and dissolved in CH_2Cl_2. Gaseous HCl was bubbled through this solution for at least 30 min at 0°C with stirring followed by stirring for 1 h to precipitate the product **2a**[22,23] as a white crystalline material. The Schiff base **3a** was obtained in 88% yield by the reaction of the ketimine with L-serine benzyl ester hydrochloride salt in CH_3CN at rt according to the procedure of O'Donnell.[24] The threonine Schiff base **3b** was prepared using the same procedure, except the crude benzyl ester formed from L-threonine and benzyl alcohol in the presence of *p*-TsOH was neutralized with $NaHCO_3$ solution. Workup and crystallization afforded the L-threonine benzyl ester according to a modification of the procedure reported by Pétursson and Baldwin.[25,26] All other Schiff bases (Fig. 2) were prepared similarly according to the aforementioned procedures.

Preparation of Dipeptide Schiff Bases

The FMOC-protected dipeptide ester **2c** was prepared by coupling FMOC-L-Ser-OH and L-valine methyl ester HCl salt with HBTU/HOBt and *i*$PrNEt_2$ in CH_2Cl_2. The FMOC group was then removed by treatment with 20% piperidine in CH_2Cl_2, and the resulting dipeptide ester was acidified with 1N HCl. The crude HCl salt was reacted with 4,4′-dimethoxydiphenylketimine in CH_3CN to yield the Schiff base **3e** (Sch. 2).

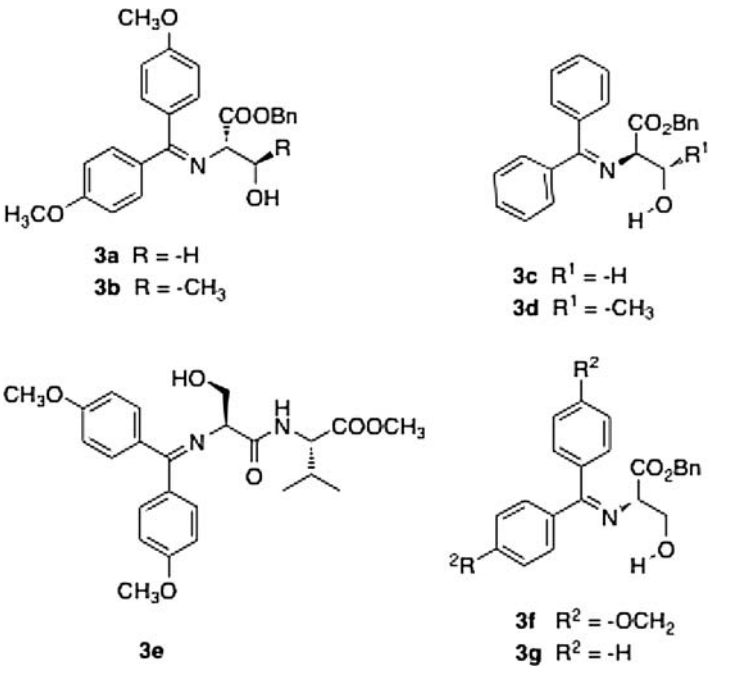
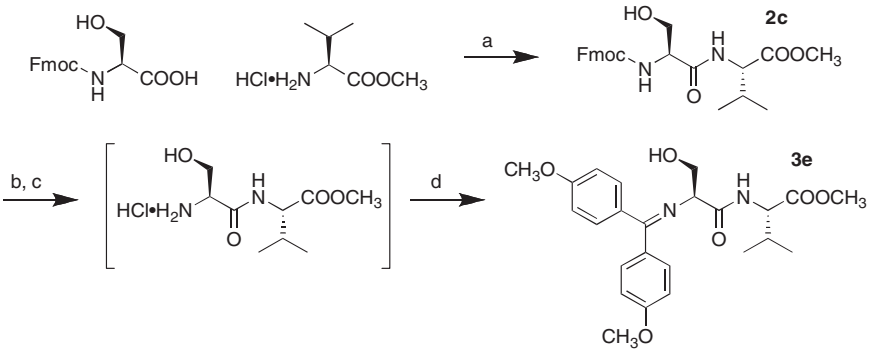


Figure 2: Schiff base acceptors.

Preparation of α- and β-acetates of Sugars[27]

Reaction of α-lactose monohydrate with Ac_2O/pyridine ($0^\circ \rightarrow$ rt) gave predominately the more stable (less reactive) α-anomer peracetate, whereas reaction with Ac_2O/NaOAc or Ac_2O/KOAc ($>100^\circ C$) resulted in the formation of



Scheme 2: Solution phase synthesis of dipeptide Schiff base **3e**. Reagents and conditions: (a) Coupling with HBTU/HOBt, *i*PrNEt$_2$, CH_2Cl_2, rt, overnight, 82%; (b) Fmoc deprotection with $C_5H_{10}NH/CH_2Cl_2$, rt, 1 h; (c) CH_3OH/HCl; (d) Ar_2C = NH, CH_2Cl_2, rt, 16 h, 21% over 3 steps b–d.

Table 1: Acetylation of sugars

Sugar	Reagents	Temperature (°C)	Reaction time (h)	Yield (%)	β/α[a]
α-D-Glucose	Ac2O/pyridine	0→rt	24	93	0.07
D-Xylose ($\alpha + \beta$)	Ac2O/pyridine	0→rt	24	83	0.07
D-Xylose ($\alpha + \beta$)	Ac2O/KOAc	140	0.1	50	33
D-Mannose ($\alpha + \beta$)	Ac2O/pyridine	0→rt	24	98	0
α-Lactose	Ac2O/pyridine	0→rt	24	87	0.10
α-Lactose	Ac2O/ZnCl2	rt	24	97	0.32
α-Lactose	Ac2O/NaOAc	105	0.25	94	4.0
α-Lactose	Ac2O/KOAc	140	1.0	86	5.9
Maltose ($\alpha + \beta$)	Ac2O/NaOAc	105	0.25	92	5.0

[a]Determined by ^{1}H NMR.

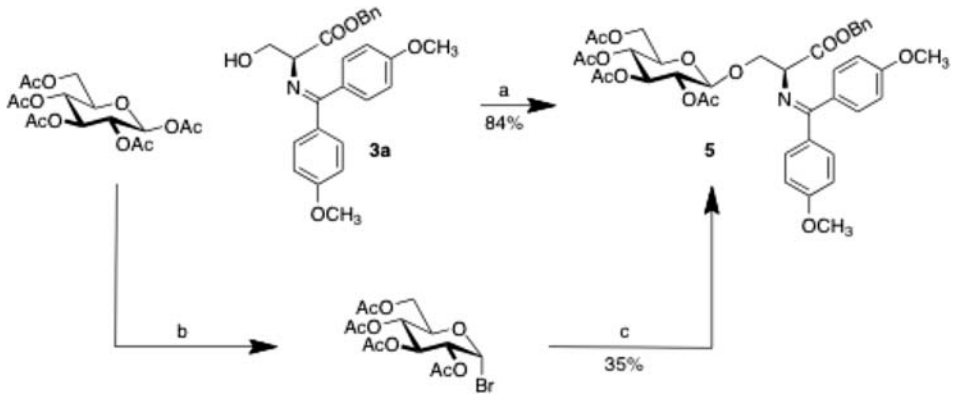
the more reactive β-anomer as the major product. Katsuraya et al. had already shown that acetylation of oligosaccharides with KOAc as a catalyst gave the highest β/α ratio.[28] The results are summarized in Table 1.

Schiff base glycosylation

The Schiff base **3a**, acting as an acceptor, was reacted with carbohydrate peracetate donors in the presence of $BF_3{\cdot}OEt_2$ at rt according to Scheme 3. These results can be compared with those using the previously published Koenigs-Knorr method (Sch. 3)[4] with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide. The glycoside products and yields are given in Tables 2 and 3. In all cases, the major anomer was isolated, and the tabulated yields are for the anomerically pure glycosides. In Table 3, the difference in reactivity between α- and β-peracetates is illustrated using both the serine- or threonine-derived Schiff bases. This reaction was further extended to disaccharides (Table 4). The glycoside Schiff bases were purified by flash SiO_2 column chromatography and analyzed by ^{1}H NMR, ^{13}C NMR, COSY, HSQC, and HMBC spectroscopic techniques.

Microwave-assisted glycosylation of Schiff bases

Most of the glycosylation reactions took at least 40 h to react to completion, and appreciable racemization of the amino acid moiety was also detected (Tables 5 and 6). The reactions were then subjected to microwave conditions and products examined by HPLC after very short reaction times (<3 min). A commercial 1000W kitchen microwave was used to heat the samples. Temperature control was provided by immersing the sealed reaction vessels in ice water. We estimated the reaction temperatures to be 40° to 60°C by measuring the temperature of several reactions upon completion of the glycosylation reactions. The results are provided in Tables 5 and 6. Glycosides (17–21, 26–27,



Scheme 3: Direct glycosylation of acetobromoglucose versus Koenigs-Knorr with the Schiff base acceptor **3a**. (a) $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, 24 h, 84%; (b) HBr, $HOAc/Ac_2O$, rt, 1 h; (c) AgOTf, CH_2Cl_2, rt, 24 h, 35%.

Fig. 3) from D-serine were included to compare the retention times with those from L-serine on a chiral column.[29] The products were purified by flash column chromatography using silica gel and analyzed by ^1H NMR, ^{13}C NMR, COSY, HSQC, and HMBC spectroscopy.

The reaction of β-D-glucose peracetate with the Schiff base **3a** with $BF_3{\cdot}OEt_2$ promotion in a microwave was further investigated to determine the effect of the solvent on racemization. The results are summarized in Table 7.

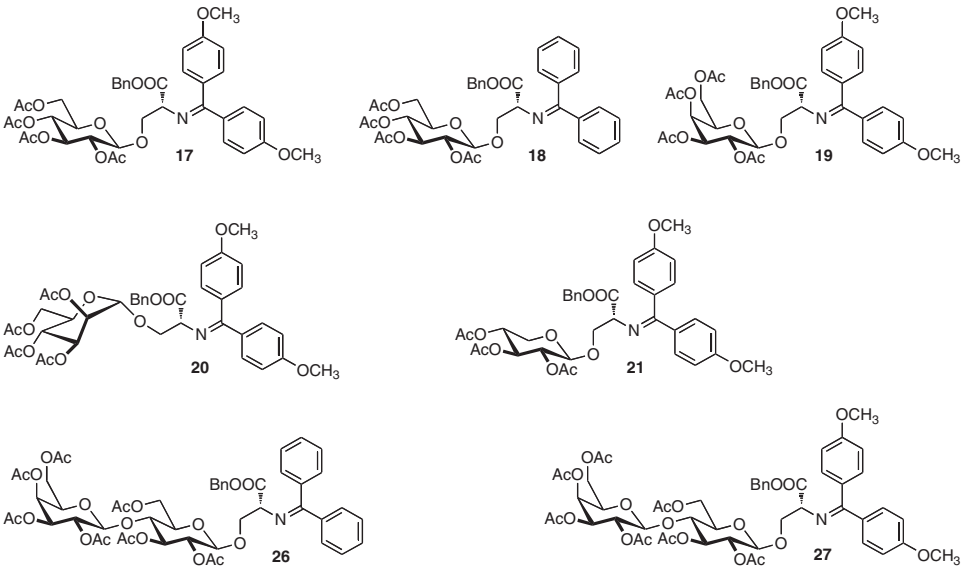
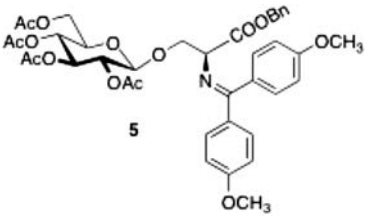
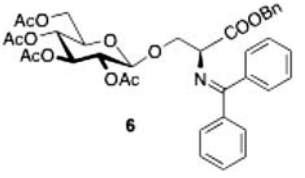
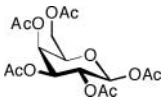
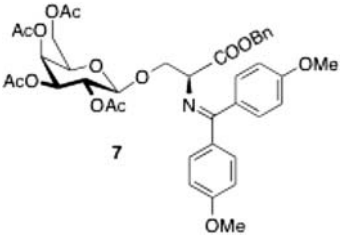
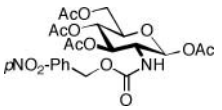
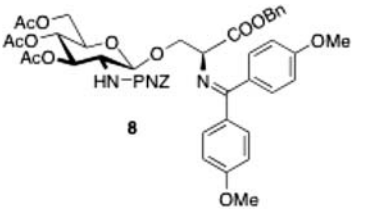
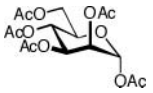
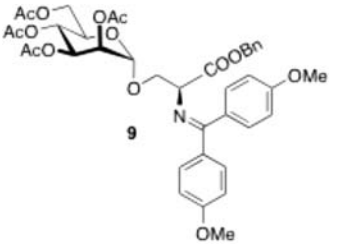


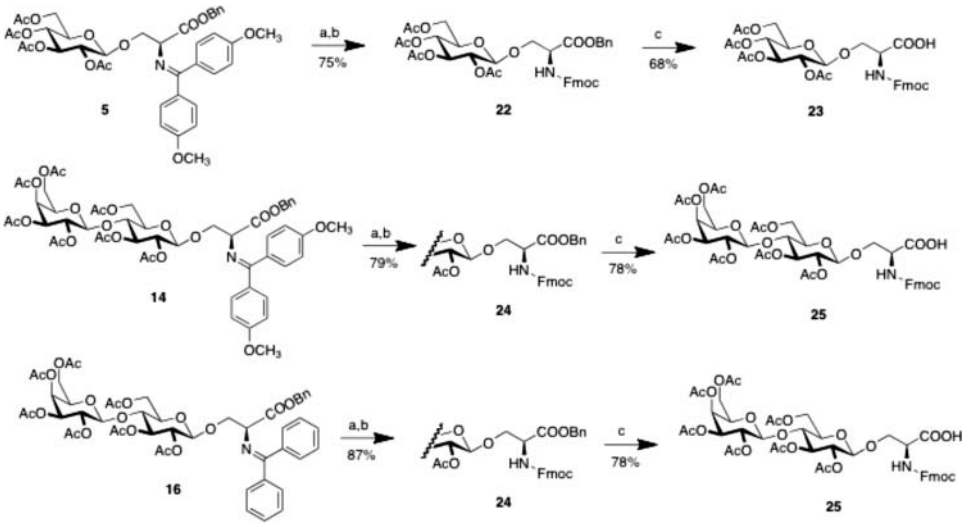
Figure 3: D-Serine Schiff base glycosides.

Table 2: Glycosylation yields using carbohydrate peracetates

Donor	Reaction time	Product	Isolated yield
	24 h	 **5**	84%
	30 h	 **6**	82%
	40 h	 **7**	64%
	48 h	 **8**	55%
	40 h	 **9**	83%

Imine Hydrolysis with Citric Acid and N-protection with 9-fluorenylmethylchloroformate (FMOC) Group

Selective removal of the imine was smoothly effected by citric acid and the $-NH_2$ group was then reprotected with FMOC (Sch. 4). Finally, deprotection by



Scheme 4: (a) Citric acid (10 equiv), H_2O, THF, 2 h; (b) FMOC-Cl (1.2 equiv.) in CH_2Cl_2 added dropwise over 20 min, DIEA (1.2 equiv.) 0°C; (c) 1 Atm. H_2\10% Pd-C EtOAc:CH_3OH (3:1) 2 h at rt.

hydrogenolysis cleaves the benzyl ester to provide the required glycosyl amino acids for FMOC peptide synthesis in excellent yield.

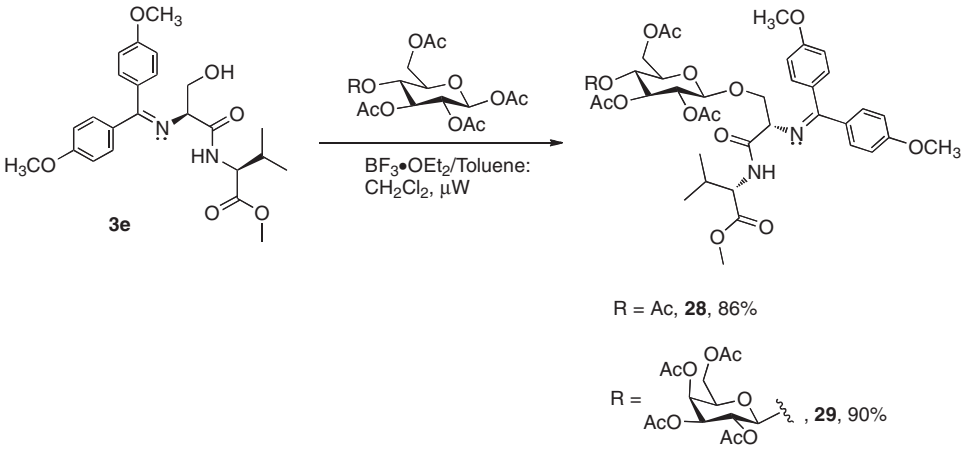
Glycosylation of the Dipeptide Schiff Base

The dipeptide Schiff base **3e** was then reacted with β-D-glucose penta-acetate and β-lactose under microwave conditions in the presence of $BF_3{\cdot}OEt_2$ to provide glycosides **28** and **29** in high yield as shown in Scheme 5. The products were analyzed by ^{1}H NMR, ^{13}C NMR, DQF-COSY, HSQC, and HMBC spectroscopic techniques after purification by flash column chromatography using silica gel.

DISCUSSION

Ring-chain Tautomerism in Benzophenone Schiff Bases

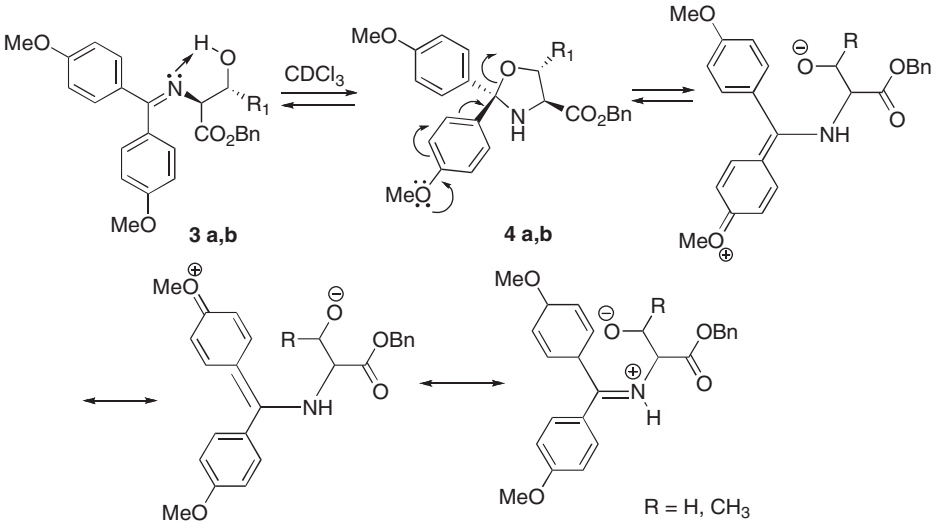
The reversible addition of a hydroxyl group to an imine double bond, also known as ring-chain tautomerism, is a well-known process of the Schiff bases of amino alcohols and has been studied extensively.[30–32] This is an *endo-trig* cyclization, which is disfavored according to the rules proposed by Baldwin.[33] The ring-chain tautomerism of benzophenone Schiff bases derived from serine/threonine has not been studied in detail. Immediately after formation, the Schiff base **3** undergoes tautomerization to give the oxazolidine **4** (Sch. 6). The NMR spectral data show that the open form (**3**) and the oxazolidine are approximately in equal proportions at equilibrium for the serine-derived Schiff



Scheme 5: Dipeptide glycosylation.

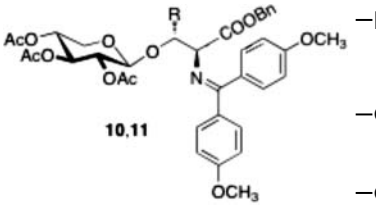
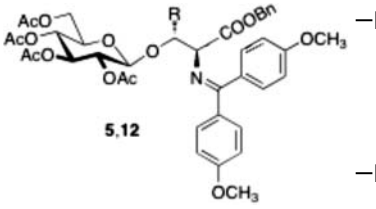
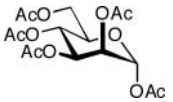
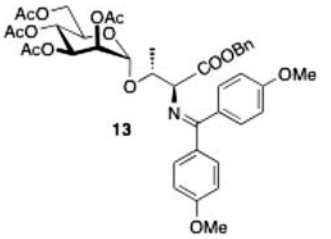
base (Fig. 4a). The tautomeric ratio determination was based on the integrals of well-separated protons; the ring protons of the *p*-methoxy compounds are well-separated doublets (ca 6.75–7.65 ppm) in the 500-MHz ^{1}H NMR spectra. In addition, for the threonine Schiff bases the methyl protons on the C^{β} position are also well-separated doublets at ca 1.13 ppm for the chain and at ca. 1.30 ppm for the ring. Using a combination of 2D COSY.

HSQC, and HMBC, the oxazolidine quaternary carbon (ca 100.61 ppm) is coupled to the aromatic protons in 1–3 bond correlations (ca 7.53, 7.38 ppm) as



Scheme 6: Ring-chain tautomerism of the Schiff bases.

Table 3: Glycosylation with α- versus β-carbohydrate peracetates

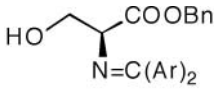
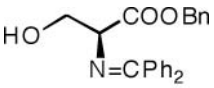
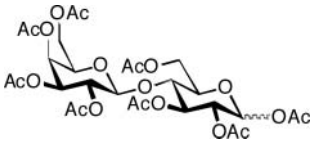
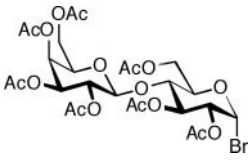
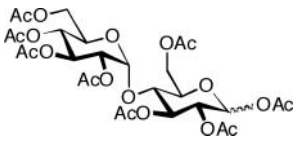
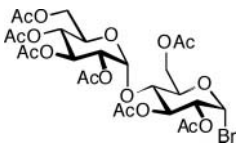
Donor	α:β	Reaction time	Product	R	Isolated yield
	14:1	40 h	 **10,11**	—H (**10**)	76%
	14:1	48 h		—CH_3 (**11**)	29%
	1:>33*	37 h		—CH_3 (**11**)	66%
	14:1	48 h	 **5,12**	—H (**5**)	trace
	1:>33*	24 h		—H (**5**)	84%
	14:1	48 h	 **13**	—CH_3 (**12**)	trace
	1:>33*	48 h		—CH_3 (**12**)	34%
	>33:1*	48 h		—CH_3 (**13**)	50%

*33:1 is the limit of detection using NMR.

shown in Figure 5 for compound **4a**. Likewise the open form of **3a** exhibits the quaternary carbon (ca 171.98 ppm) coupled to the aromatic protons (ca 7.59, 7.015 ppm) in 1–3 bond correlations.

In the case of L-threonine, the oxazolidine predominates (64.4%), suggesting that the presence of the methyl group at the C^{β} position has a strong effect on the tautomer population. This is also supported by the Schiff base without substituents on the aromatic rings in which the proportion of the oxazolidine is 91.4% for threonine compared to 76.8% of the Schiff base derived from serine. This is closely related to the *gem*-dialkyl (Thorpe-Ingold) effect,[34–36] which is defined by an increase in both rate and equilibrium constants of cyclization reactions resulting from the introduction of substituents in the linking chain. The effect is attributed to increased strain and a reduction in entropy of rotation in the open-chain compound.

Table 4: Glycosylation with disaccharide donors

Acceptor			
 Ar = *para*-MeO-Ph **3a**		 **3c**	
Disaccharide donor	α:β	Purified yields of β glycosides	
	1:4	69% (**14**)	61% (**16**)
	1:5.9	73% (**14**)	66% (**16**)
	—	68% (**14**)	65%* (**16**)
	1:5	66% (**15**)	—
	—	51% (**15**)	40%* (**15**)

*Mitchell et al.[4]

An interesting observation is made with the Schiff base with *p*-methoxy groups in which the proportion of the open form is significantly increased (Fig. 4a) for both serine and threonine. These results further establish clearly the positive inductive effect of the methoxy groups on the aromatic rings of the Schiff base. A similar observation was made with the Schiff bases of amino alcohols in which increasing the electron-withdrawing effect of substituents on the aryl group at the *para*- or *meta*-position shifts the equilibrium toward the cyclic form.[37]

Another observation worth noting in the 2D COSY spectrum in Figure 5 is the four clearly discernable spin systems in the aromatic region belonging

Table 5: RT and microwave-assisted glycosylations of monosaccharides

Donor	Acceptor	Reaction conditions	Time	Yield	HPLC %L
β-D-Glc(OAc)$_5$	**3a**	rt, CH_2Cl_2	24 h	84%	84%
β-D-Glc(OAc)$_5$	**3a**	-78°C-rt, CH_2Cl_2	51 h	63%	88%
β-D-Glc(OAc)$_5$	**3a**	μW, CH_3CN	1.75 min	63%	95%
β-D-Glc(OAc)$_5$	**3f**	rt, CH_2Cl_2	40 h	84%	81%
β-D-Glc(OAc)$_5$	**3f**	μW, CH_3CN	2.25 min	65%	97%
β-D-Glc(OAc)$_5$	**3c**	rt, CH_2Cl_2	30 h	82%	100%
β-D-Glc(OAc)$_5$	**3c**	μW, CH_3CN	2.0 min	41%	100%
β-D-Glc(OAc)$_5$	**3g**	μW, CH_3CN	2.0 min	56%	100%
β-D-Xyl(OAc)$_4$	**3a**	μW, CH_3CN	2.25 min	69%	90%
β-D-Xyl(OAc)$_4$	**3f**	μW, CH_3CN	2.25 min	62%	95%
α-D-Xyl(OAc)$_4$	**3a**	μW, CH_3CN	2.25 min	54%	92%
α-D-Man(OAc)$_5$	**3a**	μW, CH_3CN	2.25 min	38%	89%
α-D-Man(OAc)$_5$	**3f**	μW, CH_3CN	2.25 min	56%	92%

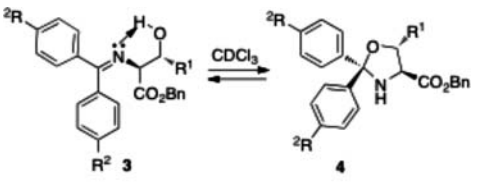
Table 6: RT and microwave-assisted glycosylation with hepta-O-acetyl-β–lactose

Donor	Acceptor	Reaction conditions	Time	Yield	HPLC %L
β-Lac(OAc)$_8$	**3a**	rt, CH_2Cl_2	48 h	82%	91%
β-Lac(OAc)$_8$	**3a**	μW, CH_3CN	2.25 min	68%	96%
β-Lac(OAc)$_8$	**3f**	rt, CH_2Cl_2	48 h	82%	91%
β-Lac(OAc)$_8$	**3f**	μW, CH_3CN	2.25 min	52%	98%
β-Lac(OAc)$_8$	**3c**	μW, CH_3CN	2.25 min	70%	100%
β-Lac(OAc)$_8$	**3c**	rt, CH_2Cl_2	48 h	67%	100%
β-Lac(OAc)$_8$	**3g**	μW, CH_3CN	2.25 min	62%	100%

Table 7: Solvent effects on glycosylation

Entry	Solvent	Reaction conditions	HPLC (L-isomer)
1	CH_2Cl_2/toluene (1:3)	0.5 h, 60°C	91%
2	CH_2Cl_2/toluene (1:3)	1 h, 60°C	91%
3	CH_2Cl_2/toluene (1:3)	3 h, 60°C	92%
4	CH_2Cl_2/toluene (1:3)	2.25 min, μW	87%
5	CH_2Cl_2/toluene (1:3)	2.25 min, μW	95%
6	Toluene	2.25 min, μW	91%
7	CH_3CN	1.75 min, μW	94%
8	CH_3CN	2.25 min, μW	95%
9	CH_3CN	2.25 min, μW	96%

μW = Microwave oven.



	R^1	R^2	3	4
a	H	OCH_3	52%	48%
b	CH_3	OCH_3	35.6%	64.4%
c	H	H	23.2%	76.8%
d	CH_3	H	8.6%	91.4%

Figure 4a: Ring-chain tautomerism and tautomer populations of Schiff bases.

	R^1	R^2	3	4
f	H	OCH_3	54%	46%
g	H	H	22%	78%

Figure 4b: Ring-chain tautomerism and tautomer populations of Schiff bases derived from D-serine.

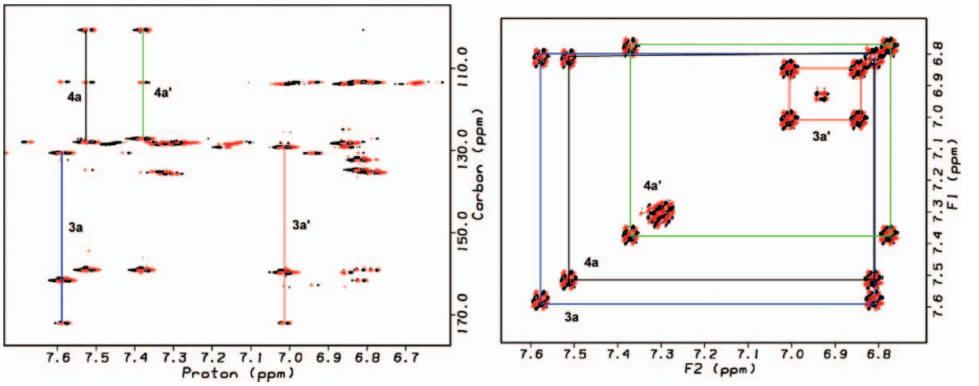


Figure 5: HMBC and COSY spectra of **3a** and **4a** in the aromatic region, and a and a′ protons on the aromatic rings of each tautomer in a 1–3 bond correlation to the quaternary carbon.

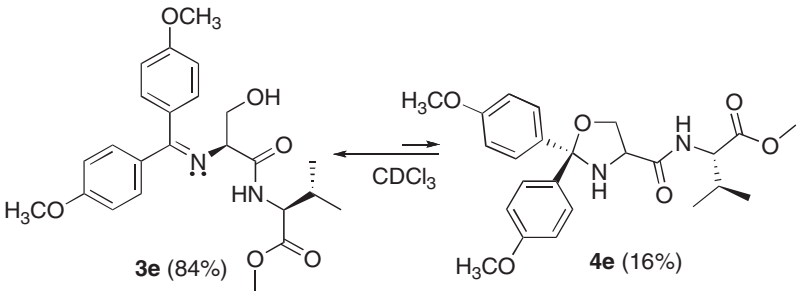


Figure 6: Elongation of the chain shifts the equilibrium to the left, favoring structure **3e**.

to the two tautomers. These data indicate that the two aromatic groups are in different chemical environments, corroborating the results of Wijayaratne and coworkers in which the N—H bond was shown to be directed toward the center of a phenyl ring on an adjacent molecule in the x-ray crystal structure of the benzophenone Schiff base of methyl L-threoninate.

On the other hand, chain elongation shifts the equilibrium to the left, favoring the open form as shown in Figure 6. On crystallization from ethyl acetate/hexanes at 0°C, only compound **3e** was isolated and its x-ray crystal is given in Figure 7. Further, the two aromatic groups are orthogonal to each other in agreement with the NMR results. The hydrogen bonding network

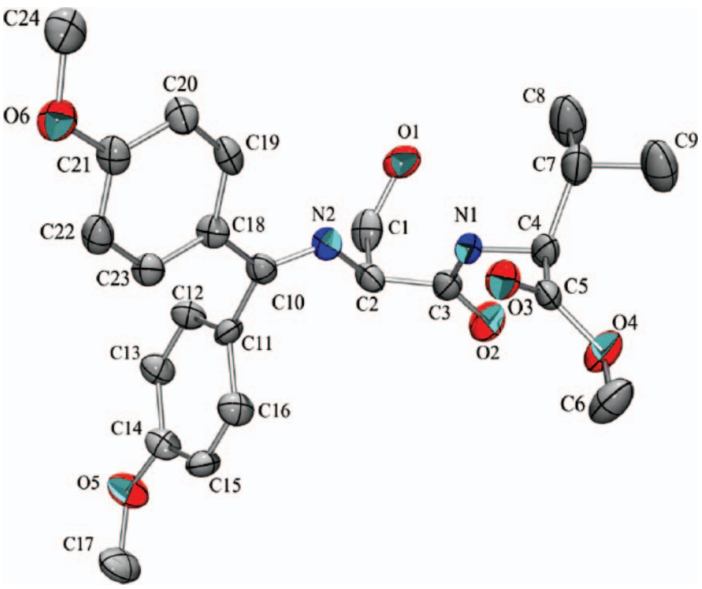


Figure 7: The molecular structure of **3e** with displacement ellipsoids at the 50% probability level. Hydrogen atoms have been omitted.

shows that the amide H (N1) is bonded to the lone pair of the imine nitrogen (N2) and the hydroxyl H (O1) is hydrogen bonded to the amide carbonyl (C5—O3) of a neighboring molecule of the compound 3e. A possible explanation for the equilibrium favoring structure **3e** is that whereas carbon C10 is electron rich due to the positive inductive effect of the *para*-methoxy groups, the hydrogen bonding pattern from the imine nitrogen (N2) favors the amide H (N1) rather than the hydroxyl H (O1). This has the overall effect of decreasing the distance between O1 and C10 for cyclization to occur. The compound adopts an extended conformation and the molecular geometry is largely unexceptional. This conformation is given added stability by an intramolecular N—H···N=C hydrogen bond; O—H···O hydrogen bonding parallel with the a axis, as shown in Figure 7; and C—H···π interactions found within the crystal packing, although there is no evidence of face-to-face aromatic stacking. The N(1)—H(1)···N(2) hydrogen bonding distance is 2.18(7) Å, whereas the O(1)—H(1)···O(2A) hydrogen bonding distance is only 1.83(8) Å and the distance of N(1)—N(2) is 2.630(8) (Table 8). This suggests that the interactions are quite strong when compared to a normal bond length of 1.451(8) Å for N(2)—C(2).

Schiff Base Glycosylation—Neighboring Group Participation Versus the Anomeric Effect

The reaction of the carbohydrate peracetate donors with the serine-derived Schiff base provided the glycosides in high yields. For the threonine-derived Schiff base moderate to low yields were obtained because it is a 2° alcohol in which sterics seem to dictate its lower reactivity. The anomeric configurations[38] of the acetates were confirmed by the one-bond coupling constants $^1J_{\text{C1-H1}} \approx 160$–$170$ Hz for the α-glycosides from the 2D HMBC spectra. An interesting reactivity trend emerged between the α- and β-acetates. One might reasonably assume that since either anomeric acetate should provide the same

Table 8: Hydrogen bonds for compound **3e** (Å and °)

D—H···A	d(D—H)	d(H···A)	d(D—A)	<(DHA)
O(1)—H(1O)···O(2A)	0.87(8)	1.83(8)	2.702(8)	178(7)
N(1)—H(1N)···N(2)	0.90(7)	2.18(7)	2.630(8)	111(5)
C(6)—H(6B)···O(1B)	0.98	2.55	3.354(10)	139
C(17)—H(17C)···O(3C)	0.98	2.51	3.400(10)	151
C(20)—H(20)···O(3A)	0.95	2.46	3.220(9)	137

Symmetry operations for equivalent atoms: A: x−1, y, z; B: x+1, y−1, z; C: x, y+1, z−1.

oxonium ion under the influence of a Lewis acid, the anomeric ratio would have no bearing on the course of the reaction. This assumption seems to be invalid.

From Table 2, β-D-glucose penta-acetate reacted with the L-serine Schiff base **3a** in CH_2Cl_2 at rt to form glycoside **5** in 84% yield, whereas the α-anomer was completely unaffected under the same reaction conditions (Table 3). Reaction of the L-threonine Schiff base (**3b**) produced glycoside **12** in 34% yield. Acetylation of D-mannose with acetic anhydride/pyridine at 0°C rt (Table 1) gave the α-peracetate exclusively as the major product, which upon reaction with **3a** resulted in the formation of the α-glycoside **9** in 83%. The pentose-derived D-xylose tetraacetate (α:β = 14:1, Table 3) reacted with **3a** to form 76% of the glycoside **10**. However, upon reaction of the same peracetate with **3b**, only 27% of **11** was obtained; the unreacted starting materials were recovered, but not used in calculating the yield. Reaction of the tetra-acetate (α:β = 1:33) with **3b** resulted in more than double the yield (66%). This clearly demonstrates that the β-anomeric acetate is more reactive than α-anomer in the presence of the Lewis acids examined, most likely aided by neighboring group participation of the acetyl in the 2-position. Further proof is illustrated by glycosylation of peracetylated lactose and maltose (Table 4) in which higher yields were obtained when the proportion of the β-acetate was increased.

It is believed that the enhanced reactivity of the β-glycosides is mostly due to participation of the neighboring *trans*-acetate, but there may also be a significant β-effect.[39] Qualitatively, the β-effect was explained in terms of the interaction of the lone pairs resulting in increased nucleophilicity due to the generation of a "new" highest occupied molecular orbital (HOMO). Strictly speaking, the β-glycoside experiences no anomeric effect and one γ-repulsion O-2-O-1 (Fig. 8), while the α-glycoside does experience the anomeric effect, and still experiences a γ-repulsion. This is also true for the α-mannoside (Tables 2 and 3), which experiences the anomeric effect and one γ-repulsion O-2-O-1, hence showing good reactivity toward the Schiff base. Hydrogen bonding can occur in protic solvents, resulting in small lone pair interactions. Hence, the anomeric effects are predicted to be more pronounced in nonpolar, aprotic solvents. Hudson and Dale[40] also demonstrated that β-glucose acetylates more readily than the α-anomer in 1915.

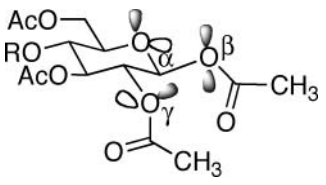
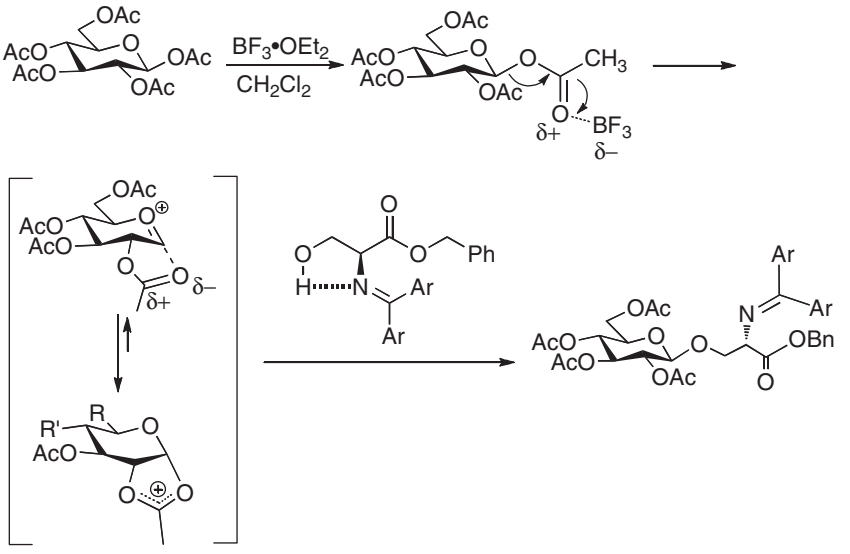


Figure 8: Consequence of the "β-effect."

Our results show that the α-xylose tetraacetate has good reactivity toward the serine-derived Schiff base, but lower reactivity with the threonine Schiff base as indicated by the yields. The difference can clearly be seen on reaction with the β-anomer, where the yield was more than doubled with the threonine Schiff base. Similar observations have been made with the penta-O-acetyl derivatives of β-D-glucopyranose and β-D-galactopyranose, which reacted rapidly at 0°C in ethyl mercaptan using $ZnCl_2$ as a catalyst to yield ethyl tetra-O-acetyl-1-deoxy-1-thio-β-D-glycopyranosides; the α-forms of these sugar acetates reacted only very slowly.[41] Further studies by Lemieux et al.[42] demonstrated that penta-O-acetyl-β-D-glucopyranose reacted very rapidly with $TiCl_4$ to yield the unstable tetra-O-acetyl-β-D-glucopyranosyl chloride, whereas the α-penta-acetate was quite stable under the same reaction conditions. Mechanistically, the reaction proceeds as shown in Scheme 7. The last three steps in the syntheses included hydrolysis of the imine by citric acid (mild acid), protection of the free amine by the FMOC group, and hydrogenolysis on Pd-C, which proceeded in excellent yields.

Both rt and microwave-assisted glycosylation reactions with the Schiff base **3a** resulted in racemized products (Tables 5 and 6). However, with the Schiff base **3c,** no racemization was detected. And finally, changing the solvent from the less polar toluene/CH_2Cl_2 to the more polar CH_3CN resulted in a small decrease in racemization (Table 7). Acetonitrile is known to form a complex with the oxocarbenium ion intermediate, hence affecting the outcome



Scheme 7: Mechanism of glycosylation with Schiff base.

of glycosylation reactions.[43] Presumably, the more polar CH_3CN can also promote enhanced enolization of the Schiff base esters, leading to epimerization of the amino acid. It is noteworthy that the dipeptide Schiff base **3e** does not show any epimerization.

CONCLUSIONS

In retrospect, this study clearly shows that Schiff bases are excellent glycosyl acceptors. This direct glycosylation procedure is ideal for the stereoselective synthesis of amino acid glycosides for peptide synthesis. The study has also demonstrated the difference in reactivity between α- and β-peracetylated carbohydrate donors in glycosylation reactions. Consequently, the β-peracetylated carbohydrate donors may be ideal candidates for glycoside syntheses at larger scales. These results further establish the positive inductive effect of the methoxy groups on the aromatic rings of the Schiff bases, and that the tautomer population of the Schiff bases depends on the substituents on the aromatic rings. The hydrogen bonding pattern from the imine nitrogen (N2) favors the amide H (N1) rather than the hydroxyl H (O1) in the dipeptide Schiff base **3e** according to the x-ray crystal structure; hence, cyclization is not favorable. Glycosylation with the dipeptide Schiff base shows the usefulness of this method in the preparation of peptide building blocks. Finally, the last three steps of the synthesis—selective removal of the imine by citric acid, reprotection of the $-NH_2$ group with the FMOC group, and deprotection of the benzyl ester by hydrogenolysis—provided required glycosyl amino acids for FMOC peptide synthesis in good yields.

EXPERIMENTAL SECTION

General Methods

All solvents for air- and moisture-sensitive reactions were freshly distilled before use. Methylene chloride, CH_3OH, and CH_3CN were distilled over CaH_2 under an atmosphere of argon. THF was dried and deoxygenated over $Ph_2C=O/Na^{\circ}$-K°. The *p*-methoxybenzonitrile and 4-bromoanisole were distilled in vacuo prior to use. All other reagents and solvents, which were purchased from commercial sources, were used directly without further purification. The ^1H and ^{13}C NMR spectra were recorded on Varian 300, Bruker 500, and Bruker 600-MHz spectrometers in $CDCl_3$ or d_6DMSO. The 2D experiments, COSY, HSQC, and HMBC, were obtained at 500 or 600 MHz. Chemical shifts are reported relative to Me_4Si (δ_H 0.0), $CHCl_3$ (δ_C 77.0, central triplet), or d_6DMSO [δ_H 2.50 (central pentet), δ_C 39.5 (central heptet)]. Optical rotations were determined with a Jasco Model P-1010 polarimeter. Reaction products of glycosides

were determined by HPLC on a CHIRALCEL OD [250 × 4.6 mm (LxI.D.)] column using hexane/2-propanol (70/30, v/v) as the mobile phase, flow rate 0.75 mL/min, detection: UV (254 nm), temperature: rt.

Bis-(4-methoxyphenyl)-methanimine (1)[24,44]

Mg (0.76 g, 31.6 mmol) was suspended in 30 mL dry THF in a flame-dried three-neck 250 mL round-bottomed flask equipped with a stir bar under argon. Some drops of 4-bromoanisole were added, and to initiate the reaction, a crystal of I_2 was added and the solution heated to a gentle reflux (~60°C). Once the color of the I_2 had disappeared, the remaining 1-bromo-4-methoxybenzene (3.9 mL, 31.1 mmol) in 8 mL THF was added via a syringe to maintain a gentle reflux. The mixture was refluxed for 45 min. After cooling to rt, 3.75 g (28.2 mmol) of *p*-methoxybenzonitrile in 8 mL of dry THF was added over 20 min and reacted for 6 h under reflux. The reaction mixture was cooled and 4.5 mL of MeOH added to quench the reaction. After stirring for 20 min, it was concentrated to remove THF, redissolved in CH_2Cl_2, and quickly washed with H_2O in a separatory funnel to remove Mg salts. The CH_2Cl_2 layer was dried over $MgSO_4$, concentrated, and redissolved in a minimal amount of CH_2Cl_2, and Et_2O added to precipitate white shiny crystals of **1** (4.01 g, 16.62 mmol, 59% yield); mp 128–129°C, lit.[45] 129.5–130°C; R_f 0.32 (60% EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.84 (6H, s), 6.90 (4H, d, J = 9.0 Hz), 7.52 (4H, d, J = 8.5 Hz), 8.95 (NH, broad); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.3 ($2CH_3O$), 113.4 (4CH, ar), 130.0 (4CH, ar), 132.1(2C, q), 161.1 (2C-O, q), and 176.9 (C=N).

L-Serine Benzyl Ester·HCl (2a)

L-Serine (5.25 g, 50 mmol) and *p*-toluenesulfonic acid (9.46 g, 55 mmol) were suspended in $PhCH_2OH$ (25 mL) in a 250-mL round-bottomed flask equipped with a Dean Stark apparatus. Benzene (25 mL) was added and the reaction was brought to reflux for 12 h; the reaction was cooled to rt and concentrated. The sample was then redissolved in 5% $NaHCO_3$ solution and extracted with i-PrOH/$CHCl_3$ (1:4, 3 × 50 mL), dried over $MgSO_4$, filtered, and evaporated to a residue. The residue was dissolved in 125 mL of CH_2Cl_2 and HCl gas bubbled into the solution at 0°C for 30 min, followed by stirring for 1 h. The precipitated white solid was washed with diethyl ether and recrystallized from *i*-PrOH/CH_3OH (13:1) according to the procedure of Holden et al.[13] Yield 6.06 g (26.2 mmol, 52.3%, over two steps); mp 170–171°C, $[\alpha]^{23.3}_D = -4.35°$ (c 1.1, MeOH); ^{1}H NMR (d_6DMSO, 500 MHz) δ 3.87 (d, $J_{\alpha,\beta}$ = 3 Hz, 2H), 4.14 (t, $J_{\beta,\alpha}$ = 3 Hz, 1H), 5.21 (s, 2H), 5.70 (1H, brs), 7.36 (m, 5H, ar); ^{13}C NMR (d_6DMSO, 500 MHz) δ 54.6 (β-CH_2), 59.5 (α-CH), 66.9 (CH_2Ph), 127.9 (CH, ar), 128.2 (2CH, ar), 128.4 (2CH, ar), 135.3 (C, q), and 168.0 (—COO—).

L-Threonine Benzyl Ester·HCl Salt (2b)

L-Threonine (4.0 g, 34 mmol) and *p*TsOH acid monohydrate (7.10 g, 38 mmol) were reacted with benzyl alcohol (40 mL) in 50 mL dry benzene using a Dean-Stark apparatus according to the procedure of Pétursson and Baldwin.[16] Yield 5.004 g (23.9 mmol, 71.3%); mp 52–54°C; $[\alpha]^{25.5}_{D} = -19.3°$ (c 2.1, CH_3OH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.20 (d, $J_{\beta,\gamma} = 6.5$ Hz, 3H), 2.30 (broad, 3H), 3.29 (d, $J_{\beta,\alpha} = 5.0$ Hz, α-H), 3.91 (m, β-H), 5.17 (s, 2H), 7.33–7.36 m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.7 (γ- CH_3), 59.9 (β-CH_2), 66.9 (CH_2Ph), 68.2 (α-CH), 128.2 (2CH, ar), 128.4 (CH, ar), 128.6 (2CH, ar), 135.3 (C, q), and 173.9 (−COO−).

L-Threonine benzyl ester (1.35 g, 6.45 mmol) was dissolved in CH_2Cl_2:CH_3OH (3:1) and HCl gas bubbled through the solution with stirring at 0°C for 1 h. The solvent was removed by rotary evaporation; then on addition of CH_2Cl_2 and diethyl ether, white crystals of the salt were precipitated and filtered to provide 1.31 g (5.33 mmol, 83%) of **2b**; mp 125–128°C, lit.[46] 127–128°C; $[\alpha]^{27.7}_{D} = -27.38°$ (c 1.0, CH_3OH),lit.[34] $[\alpha]^{22}_{D} = -11.1°$ (c 10, EtOH);^{1}H NMR (d_6DMSO, 500 MHz) δ 1.21 (d, $J_{\beta,\gamma} = 6.5$ Hz, 3H), 3.50 (d, $J_{\alpha\text{H-NH}} = 12.0$, 2H, NH_2), 3.96 (d, $J_{\beta,\alpha} = 3.5$ Hz, 1H), 4.16 (m, H), 5.21 (s, 2H), 5.75 (OH, brs), 7.32–7.43 (m, 5H, ar); ^{13}C NMR (d_6DMSO, 125 MHz) δ 20.0 (γ-CH_3), 58.1 (β-CH_2), 65.3 (α-CH), 67.0 (CH_2Ph), 128.1 (2CH, ar), 128.2 (CH, ar), 128.4 (2CH, ar), 135.2 (C, q), and 168.0 (−COO−).

D-Serine Benzyl Ester·HCl (2c)

This was synthesized according to the procedure reported by Maclaren.[47] Starting with 2.65 g (25 mmol, 1.0 equiv.), D-serine provided 4.4 g (76%) of compound **2c** as white crystals: mp 179–181°C; $[\alpha]^{25.1}_{D} = +11.93°$ (c 1.5, MeOH); ^{1}H NMR (d_6DMSO, 500 MHz) δ 3.47 (brs, NH_2), 3.88 (d, $J_{\alpha,\beta} = 3$ Hz, 2H), 4.15 (t, $J_{\beta,\alpha} = 3.5$ Hz, 1H), 5.21 (s, CH_2Ph), 5.71 (brs, 1OH), 7.31–7.34 (m, 5H, ar); ^{13}C NMR (d_6DMSO, 125 MHz) δ 54.5 (β-CH_2), 59.5 (α-CH), 66.9 (CH_2Ph), 127.9 (2CH, ar), 128.2 (CH, ar), 128.4 (2CH, ar), 135.3 (C, q), and 167.9 (−COO−).

Methyl-N-(9-fluorenylmethoxycarbonyl)-L-seryl-L-valinate (2d)

L-Valine methyl ester HCl salt (1.02 g, 6.11 mmol, 2.0 equiv.), FMOC-Ser-OH (1.0 g, 3.06 mmol, 1.0 equiv.), HOBt (0.94 g, 6.11 mmol, 2.0 equiv.), and HBTU (2.32 g, 6.11 mmol, 2.0 equiv.) were weighed into a 250-mL round-bottomed flask and 5.5 mL DIEA (30.6 mmol, 10.0 equiv.) added. Dichloromethane (15 mL) was then added and stirred at rt overnight. The reaction mixture was then washed two times with conc. $NaHCO_3$, one time with brine, and one time with H_2O; dried over $MgSO_4$; and concentrated on a rotary evaporator. Flash chromatography with 60% EtOAc: hexanes ($R_f = 0.3$) crystallization from EtOAc: hexanes provided 1.10 g (82%) of **2d** as white crystals.

$[\alpha]^{25.2}_{D} = -35.12^{\circ}$ (c 1.0, $CHCl_3$); ^{1}H NMR ($CHCl_3$, 500 MHz) δ 0.88 (d, J = 7.0 Hz, 3H), 0.92 (d, J = 7.0 Hz, 3H), 2.18 (m, 1H), 3.50 (dd, J_1 = 9.3 Hz, J_2 = 4.48 Hz, OH), 3.69 (m), 3.72 (s, OCH_3), 4.04 (m, 1H), 4.20 (t, J = 7.0 Hz, 1H), 4.34 (m, 1H), 4.39 (d, J = 7.0, 2H), 4.51 (dd, J_1 = 9.0 Hz, J_2 = 5.0 Hz, 1H), 5.98 (d, J = 7.5 Hz, NH, FMOC), 7.11 (d, J = 8.0 Hz, NH), 7.29 (t, J = 7.5 Hz, 2H, ar), 7.38 (t, J = 7.5 Hz, 2H, ar), 7.57 (d, J = 7.5 Hz, 2H, ar), 7.74 (d, J = 7.5 Hz, 2H, ar); ^{13}C NMR ($CHCl_3$, 125 MHz) δ 17.6 (CH_3), 19.0 (CH_3), 30.7 (CH), 47.0 (CH, FMOC), 52.3 (OCH_3), 55.2 (CH), 57.5 (CH), 62.9 (CH_2), 67.4 (CH_2), 119.9 (2CH, ar), 125.0 (2CH, ar), 127.0 (2CH, ar), 127.7 (2CH, ar), 141.2 (C, q), 143.6 (C, q), 143.6 (C, q), 156.5 (−CONH, FMOC), 171.1 (−CONH−), and 172.3 (−COO−). FABMS: $C_{24}H_{28}N_2O_6$, m/z $[M + H]^+$ 441.2.

Benzyl N-*bis*-(4-methoxyphenyl)methylene-L-serinate (3a)

The procedure adopted was that of O'Donnell.[24] L-Serine benzyl ester·HCl (2a) (2.535 g, 10.5 mmol, 1.1 equiv.) and the *bis* (*p*-methoxy)-diarylketimine (1) (2.4 g, 10 mmol, 1.0 equiv.) were dried over P_2O_5 overnight in vacuo and transferred to a flame-dried 250-mL round-bottomed flask with a stir bar. The L-serine benzyl ester·HCl was ground into a fine powder before being transferred to the round-bottomed flask. Dry CH_3CN (60 mL) was added and stirring started at rt and reacted for at least 16 h. TLC showed full conversion. The reaction mixture was filtered, washed quickly with saturated $NaHCO_3$ solution, and then dried over $MgSO_4$. Finally, it was filtered, concentrated, and flash chromatographed with 55% EtOAc: hexanes: 0.1% NEt_3 to afford 3.67 g (8.75 mmol, 88%) of the Schiff base as a colorless oil; $[\alpha]^{28.1}_{D} = -75.16^{\circ}$ (c = 3.0, $CHCl_3$); R_f 0.64 (55% EtOAc: hexanes); (3a) ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.73 (brs, OH), 3.78 (s, 3H, C$\underline{H}_3$O), 3.80 (s, 3H, C$\underline{H}_3$O), 3.97 (dd, $J_{\alpha,\beta}$ = 1.5 Hz, $J_{\alpha,\beta'}$ = 4.5 Hz, 2H), 4.29 (t, $J_{\beta,\alpha}$ = 5.0 Hz, 1H), 5.15 (d, J = 9.0 Hz, 2 H, C$\underline{H}_2$Ph), 6.82 (d, J = 8.5 Hz, 2H, ar H's), 6.85 (d, J = 9.0 Hz, 2H, ar H's), 7.01 (d, J = 8.5 Hz, 2H, ar H's), 7.31 (m, 5H, ar), 7.59 (d, J = 9.0 Hz, 2H, ar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.2 (CH_3O), 55.1 (CH_3O), 64.2 (β-CH_2), 66.4 (α-CH), 66.4 (CH_2Ph), 113.2 (CH, ar), 113.7 (CH, ar), 127.9 (2CH, ar), 127.9 (CH, ar), 128.4 (CH, ar), 128.5 (CH, ar), 130.6 (CH, ar), 132.1 (C, q), 132.2 (C, q), 135.6 (C, q), 159.6 (C, q), 161.6 (C, q), 170.8 (−COO−) and 172.0 (C=N). ESIMS: $C_{25}H_{25}NO_5$, m/z $[M + H]^+$ 420.4.

(*S*)-Benzyl-2,2-bis(4-methoxyphenol)oxazolidine-4-carboxylate (4a)

^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.06 (brs, NH), 3.73 (s, 3H, C$\underline{H}_3$O), 3.75 (s, 3H, C$\underline{H}_3$O), 3.91 (dd, $J_{\alpha,\beta}$ = 7.5 Hz, $J_{\beta,\beta}$ = 12.5 Hz, 2H), 5.16 (d, J = 12.0 Hz, 2H, C$\underline{H}_2$Ph), 6.78 (d, J = 8.5 Hz, 2H, ar), 6.82 (d, J = 8.5 Hz, 2H, ar), 7.31 (m, 5H, ar), 7.38 (d, J = 8.5 Hz, 2H, ar), 7.52 (d, J = 9.0 Hz, 2H, ar); ^{13}C NMR

($CDCl_3$, 125 MHz) δ 55.1 ($2CH_3O$), 59.8 (β-CH_2), 66.4 (α-CH), 67.2 (CH_2Ph), 100.6 (C, q), 113.4 (2CH, ar), 127.1 (CH, ar), 128.2 (CH, ar), 134.7 (C, q), 135.1 (C, q), 135.3 (C, q), 159.0 (C, q), 159.0 (C, q), and 172.3 (−COO−).

Benzyl N-*bis* (4-methoxyphenyl)methylene-L-threoninate (3b)

Reaction of **1** (0.625 g, 2.6 mmol, 1.0 equiv.) and **2b** (0.70 g, 2.85 mmol, 1.1 equiv.) in 40 mL CH_3CN as described in the preparation of **3a** gave **3b** as a colorless oil(1.12 g, 2.58 mmol, 99.64%); $[\alpha]^{28.1}_D = -75.67^\circ$ (c 1.4, $CHCl_3$); R_f 0.37 (20% EtOAc: hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.13 (d, $J_{\beta,\gamma}$ = 6.5 Hz, 3H), 3.23 (brs, OH), 3.80 (s, 3H, C$\underline{H}_3$O), 3.81 (s, 3H, C$\underline{H}_3$O), 3.97 (d, $J_{\beta,\alpha}$ = 3.5 Hz, α-H), 4.32 (m, β-H), 5.13 (d, J = 12.0 Hz, C$\underline{H}_2$Ph), 6.84 (d, J = 9.0 Hz, 2H, ar), 6.85 (d, J = 8.5 Hz, 2H, ar), 6.97 (d, J = 8.5 Hz, 2H, ar), 7.29–7.35 (m, 5H, ar), 7.61 (d, J = 9.0 Hz, 2H, ar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.6 (γ-CH_3), 55.2 (CH_3O), 55.3 (CH_3O'), 66.0 (β-CH_2), 70.3 (α-CH), 66.5 (CH_2Ph), 113.3 (CH, ar), 113.8 (CH, ar), 128.1 (2CH, ar), 128.4 (CH, ar), 128.4 (2CH, ar), 129.0 (2CH, ar), 130.5 (2CH, ar), 132.1 (C, q), 135.7 (C, q), 159.6 (C, q), 161.7 (C, q), 170.9 (−COO−), and 172.1 (C=N). ESIMS $C_{26}H_{27}NO_5$, m/z $[M + H]^+$ 434.1.

(*S*)-Benzyl-2,2-bis(4-methoxyphenyl)oxazolidine-4-carboxylate (4b)

^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.29 (d, $J_{\beta,\gamma}$ = 6.5 Hz, 3H), 3.23 (brs, NH), 3.60 (d, $J_{\beta,\alpha}$ = 8.0 Hz, α-H), 3.74 (s, 3H, C$\underline{H}_3$O), 3.76 (s, 3H, C$\underline{H}_3$O), 4.09 (m, β-H), 5.16 (d, J = 12.0 Hz, 2H, C$\underline{H}_2$Ph), 6.78 (d, J = 8.5 Hz, 2H, ar), 6.80 (d, J = 9.0 Hz, 2H, ar), 7.29–7.35 (m, 5H, ar), 7.38 (d, J = 8.5 Hz, 2H, ar), 7.52 (d, J = 8.5 Hz, 2H, ar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.3 (γ-CH_3), 55.1 (CH_3O), 55.2 (CH_3O'), 67.0 (CH_2Ph), 67.1 (α-CH), 77.3 (β-CH_2), 99.7 (C, q), 113.2 (CH, ar), 113.4 (CH, ar), 127.1 (CH, ar), 127.6 (CH, ar), 128.2 (CH, ar), 128.6 (CH, ar), 135.2 (C, q), 136.5 (C, q), 137.2 (C, q), 158.8 (C, q), 159.0 (C, q), and 171.1 (−COO−).

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