Communications to the Editor

Synthesis of Carbon-Linked Glycopeptides through Catalytic Asymmetric Hydrogenation

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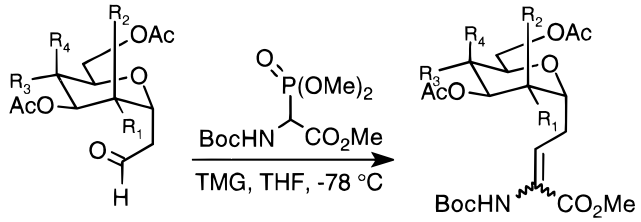
Glycopeptides play important roles in a number of cellular recognition events including tumor metastasis, immunosurveillance, and chemotaxis.[2] Carbon-linked glycopeptides are attractive synthetic targets due to their increased stability to chemical and enzymatic cleavage.[3] Additionally, *C*-glycosides demonstrate solution conformations[4] and biological activities similar to naturally occurring glycopeptides.[5] Accordingly, much effort has been invested in developing methods to efficiently construct *C*-linked glycoconjugates.[6] *We report here a concise high-yielding synthesis of enantiomerically pure* D- *or* L-C-*glycosyl serine analogs*. The key step of the synthesis is an asymmetric catalytic hydrogenation of a *C*-glycosyl enamide with the cationic rhodium-DuPHOS catalyst.

The preparation of *C*-glycosylated serine analogs has been hampered by the production of mixtures of isomers at the α-amino acid center.[7] To the best of our knowledge, only one stereoselective synthesis of this class of compounds has been published. Bednarski and co-workers[8] have prepared the *C*-linked glycopeptide analog *β*-galactose-CH_2-serine through olefination of a *C*-glycosyl aldehyde with a chiral Wittig reagent. In this case, the configuration of the amino acid center was set through the stoichiometric use of a chiral phosphorus reagent.

In the course of our studies on protein-carbohydrate interactions, we required a general concise route to either D- or L-*C*-glycosyl serine derivatives. A route relying on catalytic asymmetric hydrogenation seemed appropriate for this purpose. To this end, the DuPHOS-Rh^+ catalyst[9] presented itself as an ideal candidate due to its ability to reduce a variety of enamides with wide substrate generality and excellent chiral induction.[10]

The *C*-linked enamide esters of glucose **1**, galactose **2**, and mannose **3** were prepared in one step from the known *C*-linked aldehydes with use of modified literature procedures.[6,7] The requisite aldehydes were prepared by radical allylation of the appropriate peracetylated bromosugar according to the method of Magnusson[11] followed by ozonolysis.[12] Horner-Emmons olefination with the Boc protected phosphonate methyl ester[14] with tetramethylguanidine in THF at −78 °C for 1 h resulted in the production of the enamide precursors in good yields (79−88%).[13,14]

Scheme 1. Synthesis of *C*-glycosyl Enamide Precursors



Product	R_1	R_2	R_3	R_4	Yields
1 (Glucose)	OAc	H	OAc	H	79%
2 (Galactose)	OAc	H	H	OAc	85%
3 (Mannose)	H	OAc	OAc	H	88%

Table 1. Effect of Ligand Substitution on *de* and Yield[a]

	glucose		galactose		mannose	
ligand	% de[b]	% yield[c]	% de	% yield	% de	% yield
S,S-Me-DuPHOS	84	95	58	85	74	75
R,R-Et-DuPHOS			82	86	>95	72
R,R-n-Pr-DuPHOS	>95	83	77	97	>95	95
R,R-i-Pr-DuPHOS	NR	NR	NR	NR	NR	NR

[a] All reactions were carried out in MeOH. [b] Diastereomeric excess was determined with ^{1}H NMR (400 MHz). *R,R-n*-Pr and *R,R*-Et ligands gave products with the R configuration, the *S,S*-Me ligand gave the S configuration. [c] Yields of isolated product.

To find the appropriate catalyst precursor for the hydrogenation of the *C*-glycosyl enamide esters, it was necessary to pair the steric demands of the substrates with the size of the R groups on the DuPHOS ligand. The nature of the alkyl groups on the DuPHOS ligand was varied and optimized with respect to both diastereomeric excess (*de*) and yield of the resulting *C*-glycosylated amino acids (Table 1). The bulky *iso*-propyl DuPHOS ligand appeared to be too large to effect catalysis, and starting material was recovered in all cases. In contrast, the small methyl substituted ligand showed excellent reactivity although only moderate stereoselectivity (70-85% *de*). In methanol solvent, both the glucoside and the mannoside were produced in >95% *de* and excellent yields with use of the *n*-propyl-substituted DuPHOS ligands. The ethyl-substituted DuPHOS also gave >95% *de* when used with **3**. Alternatively,

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(13) Separation of E/Z isomers of the *C*-glycosyl enamides was unnecessary as previous work with the DuPHOS-Rh^+ catalyst[10] demonstrates that the stereochemical outcome of asymmetric hydrogenation is independent of the enamide conformation.
(14) Preparation of methyl α-(dimethoxyphosphoryl)-*N*-*tert*-butyloxycarbonylglycinate is described in the following publications: (a) Zoller, U.; Ben-Ishai, D. *Tetrahedron* **1970**, *81*, 863−5. (b) Schmidt, U.; Griesser, H.; Leitenberger, V.; Lieberknecht, A.; Mangold, R.; Meyer, R.; Riedl, B. *Synthesis* **1992**, 487−490.

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Scheme 2. Generalized Hydrogenation Reaction of *C*-Galactosyl Enamide Ester **2**

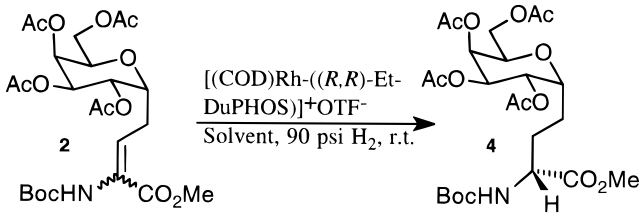

Table 2. Solvent Studies with *C*-Glycosyl Enamide Esters[a]

	galactose		mannose	
solvent	% de[b]	% yield[c]	% de	% yield
MeOH	58	85	>95	72
i-PrOH			>95	70
$PhCH_3$	>95	91	>95	91
THF	>95	92	>95	71
EtOH	66	90		
CH_2Cl_2			77	92

[a] All reactions were carried out with the *R,R*-Et-DuPHOS ligand. [b] Diastereomeric excess was determined with ^1H NMR (400 MHz). [c] Yields of isolated product.

the galactose substrate **2** was hydrogenated with only moderate diastereoselectivity.[15]

The effect of reaction solvent was examined in an attempt to increase the diastereomeric excess (*de*) for hydrogenation of **2**. The hydrogenation reaction was carried out with the (*R,R*)-Et-DuPHOS-Rh^+ catalyst precursor and at 90 psi H_2 pressure in THF, methanol, ethyl acetate, or toluene (Table 2). In either THF or toluene, the reduction of the galactose substrate **2** proceeded with *de*'s above 95% and conversions of 92% and 91%, respectively.

Hydrogenation of the mannoside substrate **3** was examined in THF, methanol, CH_2Cl_2, 2-propanol, and toluene at 90 psi H_2 with the (*R,R*)-Et-DuPHOS-Rh^+ catalyst precursor. All proceeded in greater than 95% *de* with the exception of CH_2Cl_2 which produced a *de* of 77%. Yields ranged from 70% in methanol to 91% in toluene (Table 2).

For purposes of comparison, all three enamide esters were hydrogenated with an achrial catalyst, which produced 50/50 mixtures of R and S configuration at the newly formed stereogenic center. The formation of this mixture of R and S products was somewhat surprising; apparently chirality transfer occurs solely from the DuPHOS-Rh^+ catalyst and not from the carbohydrate.

In conclusion, we have utilized a catalytic asymmetric hydrogenation for the synthesis of *C*-glycosylated serine analogs. Both D- and L-stereochemistry at the α-amino acid center can be generated in high *de* from the same enamide precursor.[16] The synthesis proceeds in greater than 45% overall yield from the corresponding peracetylated sugar, making this methodology practical for large scale preparation of *C*-glycosyl amino acids. Experiments to explore the versatility of this new methodology are underway and will be reported in due course.

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Supporting Information Available: Procedures for the preparation and hydrogenation of the *C*-glycosyl enamide esters as well as selected spectral and analytical data (4 pages). See any current masthead page for ordering and Internet access information.

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(15) It is should be noted that in all cases the diastereomeric excess was determined by ^1H NMR (400 MHz) by integrating the area of the $-CO_2CH_3$ or Boc protons. The glycosylated amino acids had very low volatility, even as the tetrasilylated derivatives, which prohibited the use of gas chromatography. HPLC also proved to be inaccessible due to excessive line broadening under a variety of conditions.

(16) The catalytic asymmetric hydrogenations of the β anomers of the *C*-glycosylated serine analogs were also examined. The β isomers of the mannose, glucose, and galactose *C*-glycosyl aldehydes were synthesized with use of modified literature procedures.[6] Reaction of these aldehydes with the Horner−Emmons reagent as described above afforded the β enamides in good yields (80−90%). The resulting enamide esters were hydrogenated with the (*R,R*)-Et-DuPHOS-Rh^+ catalyst precursor in THF for the galactose and mannose substrates, and methanol for the glucose substrate. Results paralleled those obtained with the α anomers, with the yields between 80−90% and *de* in all three cases >95%.