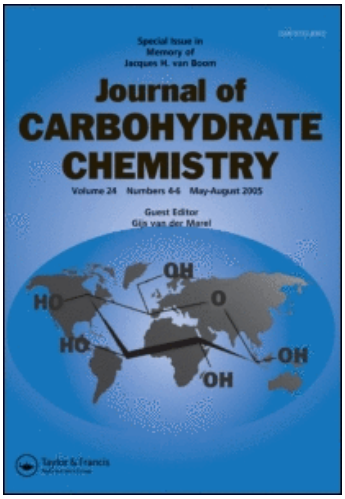

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INVESTIGATION OF THE SHARPLESS ASYMMETRIC AMINOHYDROXYLATION WITH *C*-ALLYL GLYCOSIDES

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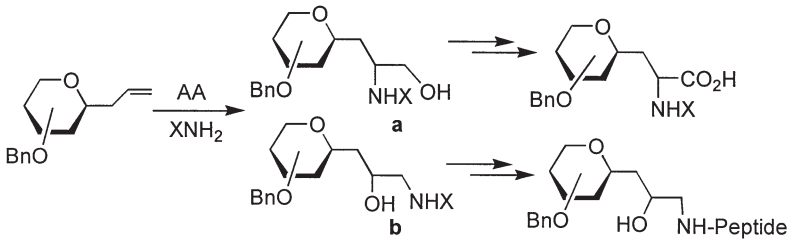
ABSTRACT

We have studied the Sharpless asymmetric aminohydroxylation on *C*-allyl glycosides in order to prepare *C*-glycosyl aminoacids or *C*-glycopeptides. The perbenzylated amino α-*C*-allyl glucoside **1** and β-*C*-allyl glucoside **2** were shown to be moderate substrates for this reaction. New *C*-glycosyl α-amino ketones were isolated after oxidation of the crude β-amino alcohols.

INTRODUCTION

The preparation of diversely functionalised *C*-glycosides is of importance because these compounds can be used as inhibitors of carbohydrate processing enzymes or as structural subunits of biologically active molecules.[1–6] Among various synthetic methods, the recent Sharpless asymmetric aminohydroxylation (AA) procedure is of particular interest for allowing the conversion of alkenes into enantiomerically enriched *N*-protected β-amino alcohols.[7–10] Briefly, this reaction has been conducted with a combination of OsO_4 (produced from $K_2OsO_2(OH)_4$), alkaloid-derived ligands, and the Li or Na salt of an *N*-halogenated sulfonamide,[7] alkyl carbamate[8,9] or amide[11] as the nitrogen source in an alcohol/water solvent mixture. Various classes of olefins including styrenes, α,β -unsaturated esters, vinyl furans,[12] vinyl phosphonates,[13] alkenyl phosphinates,[14] dienylsilanes[15] and silyl enol ethers[16] have been used as substrates, thus affording a number of biologically active compounds or their precursors. Application of this method to *C*-allyl glycosides should lead to novel functionalised *C*-glycosyl derivatives. As depicted



Scheme 1.

in Scheme 1, aminohydroxylation of the C═C bond may afford two regioisomers **a** and **b** which are suitable for further transformation into *C*-glycosyl amino acids or *C*-glycopeptides.[6, 17,18]

RESULTS AND DISCUSSION

We have employed $(DHQ)_2PYR$ as the chiral ligand and *tert*-butyl carbamate as the nitrogen source so that the Boc protecting group can be later removed selectively. The AA of **1**[19] in *n*-PrOH/water proved to be unsuccessful, presumably due to the insolubility of the substrate in such a solvent. Addition of DMF to the reaction mixture allowed partial conversion. Complete consumption of **1** was realised by repeating the procedure one more time (see experimental).

Analysis of the crude mixture (^1H and ^{13}C NMR) revealed the presence of several products: the isomeric amino alcohols **3** and **4** (^1H NMR: three singlets at 1.33, 1.34 and 1.37 ppm for the *tert*-butyl group) and presumably diols **5** (minor product) (Scheme 2). However, all our attempts to separate these compounds to ascertain the regio- and stereoselectivity failed, even after acetylation of the reaction mixture. So we decided to perform directly the oxidation (sodium hypochlorite, TEMPO and potassium bromide[9]) of the crude mixture. Further preparative thin-layer chromatography allowed us to obtain the protected α-amino ketone **6** (in 20 % overall yield) as the sole isolable compound. It was impossible to isolate the *C*-glycosyl amino acid resulting from the oxidation of **4** in any significant amount.

The aminohydroxylation of the β-*C*-allyl glycoside **2**[20] was conducted in a similar fashion. Direct oxidation of the crude mixture gave the α-amino ketone **7** (in 14 % overall yield) as the sole isolable product after preparative thin-layer chromatography.

In summary, we report herein the first example of Sharpless AA applied to *C*-glycosides. Although the *C*-allyl glycosides **1** and **2** appeared to be moderate substrates for AA, their aminohydroxylation followed by oxidation provided a straightforward access to new *C*-glycosyl α-amino ketones, albeit in moderate yield.

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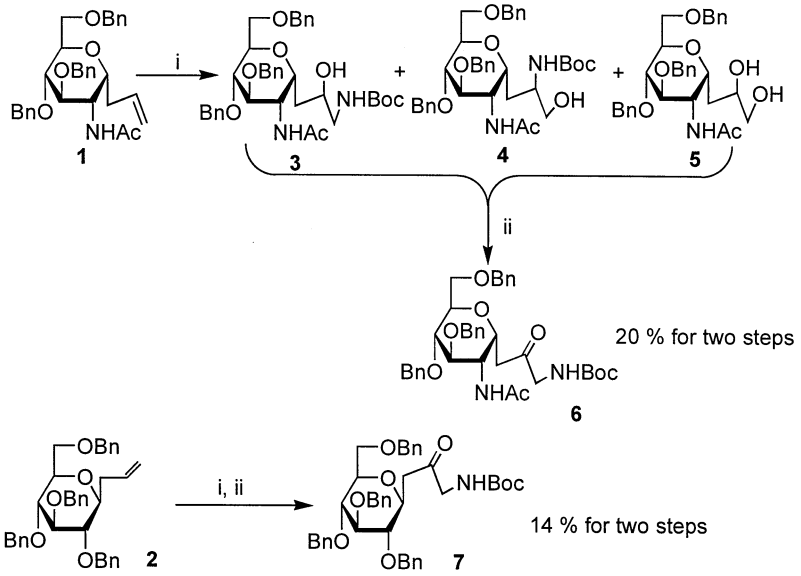
EXPERIMENTAL

General methods. Melting points were measured with a Thomas-Hoover apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AGH-250 spectrometer in $CDCl_3$ solutions. Optical rotations were measured using a Perkin-Elmer 141 polarimeter and a 10-cm cell. Microanalyses were performed at the Service de Microanalyse de l'Université Pierre et Marie Curie.

General procedure for the aminohydroxylation of *C*-allyl glycosides. A solution of NaOH (0.4 M, 0.625 mL) followed by *tert*-butyl hypochlorite (70 μL, 0.589 mmol) was added to a solution of *tert*-butyl carbamate (54 mg, 0.450 mmol) in 1-propanol (0.6 mL) and cooled to 0 °C after 5 min stirring. $(DHQ)_2Pyr$ (7.2 mg, 0.008 mmol) in 1-propanol (0.6 mL) followed by *C*-allyl glycoside (0.150 mmol) in DMF (1 mL) and $K_2OsO_2(OH)_4$ (3 mg, 0.008 mmol) in NaOH (0.4 M, 0.5 mL) were added to this cooled mixture. The reaction mixture was stirred overnight, quenched with Na_2SO_3 and extracted with AcOEt (3×15 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The same procedure was repeated once on the crude product for complete consumption of the starting *C*-glycosides.

General procedure of the oxidation of amino alcohols. The crude mixture of aminoalcohols (0.500 mmol) obtained from the aminohydroxylation reac-



Reagents and conditions: i) $K_2OsO_2(OH)_4$, $(DHQ)_2PYR$, H_2NCO_2tBu, NaOH, *t*-BuOCl, *n*-PrOH-DMF-H_2O, rt; ii) NaOCl, TEMPO, 5 % $NaHCO_3$, KBr, acetone, 0°C to rt.

Scheme 2.

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tion (vide supra) was dissolved in acetone (3 mL) and cooled to 0 °C. To this magnetically stirred solution, were added an aqueous 5 % $NaHCO_3$ solution (706 μL), KBr (2 mg, 0.017 mmol), TEMPO (26 mg, 0.166 mmol). Sodium hypochlorite (48 %, 230 μL, 1.482 mmol) was added dropwise over 10 min. After 1 h, additional aqueous NaOCl solution (115 μL, 0.741 mmol) was added dropwise over 5 min, and stirring was continued at 0 °C for 1 h and at room temperature overnight. Water (10 mL) was then added, the aqueous mixture was acidified to pH 6 with 10 % aqueous citric acid and extracted with AcOEt (3×10 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated. The crude mixture was purified by preparative thin-layer chromatography (eluent CH_2Cl_2/MeOH: 30/1) to give the corresponding α-amino ketones.

3-(2′-(*N*-Acetylamino-3′,4′,6′-tri-*O*-benzyl-2′-deoxy-α-D-*C*-glucopyranosyl)-1-*tert*-butoxycarbonylamino-propan-2-one (6). 20 % Yield from **1**: white solid, mp 105 °C, Rf 0.44 (AcOEt/hexane: 2/1), $[\alpha]_D$ +12 (*c* 1, CH_2Cl_2). ^{1}H NMR: 1.40 (s, 9H, *t*Bu), 1.81 (s, 3H, Ac), 2.40–2.60 (m, 2H, CH_2-CO), 3.54 (m, 1H), 3.63 (m, 1H), 3.70–3.86 (m, 2H, H-6′, 6″), 3.96–3.98 (m, 2H, CH_2N), 4.13–4.21 (m, 2H), 4.35–4.62 (m, 7H, H-1′, 3xOCH_2), 5.18 (m, 1H, NHBoc), 6.75 (d, 1H, *J*=9.5 Hz, NH), 7.23–7.29 (m, 15H, Ph); ^{13}C NMR: 24.5 (Ac), 29.6 (*t*Bu), 43.2 (CH_2-CO), 48.3 (C-2′), 52.2 (CH_2-N), 65.6 (C-1′), 68.8 (C-6′), 73.0, 73.1, 74.6 (CH_2); 74.1, 75.0, 76.4 (C-3′,4′,5′), 80.8 (C*q*), 128.8, 128.9, 129.0, 129.2, 129.4, 129.6, 129.8, 129.9 (Ph); 138.4, 138.5, 139.3 (C*ipso*); 156.8, 171.3, 204.8 (CO).

Anal. Calcd for $C_{37}H_{46}N_2O_8$: C, 68.71; H, 7.17; N, 4.33. Found: C, 68.60; H, 7.31; N, 4.20.

3-(2′,3′,4′,6′-Tetra-*O*-benzyl-β-D-*C*-glucopyranosyl)-1-*tert*-butoxycarbonylamino-propan-2-one (7). 14 % Yield from **2**: oil, Rf 0.29 (Et_2O/hexane: 1/1), $[\alpha]_D$ +4 (*c* 1, MeOH). ^{1}H NMR: 1.36 (s, 9H, *t*Bu), 2.48 (dd, 1H, *J*=6.8, 15.0 Hz, CH), 2.62 (dd, 1H, *J*=3.8, 15.0 Hz, CH), 3.24 (dd, 1H, *J*=8.8, 9.3 Hz, CH), 3.33 (td, 1H, *J*=2.8, 9.3 Hz, CH), 3.56–3.70 (m, 5H), 3.91 (d, 2H, *J*=4.8 Hz, CH_2N), 4.38–4.87 (m, 8H, 4xOCH_2), 5.08 (t, 1H, *J*=4.8 Hz, NH), 7.07 −7.26 (m, 20H, Ph); ^{13}C NMR: 28.8 (*t*Bu), 42.9 (CH_2-CO), 51.8, 69.1, 73.8, 75.4, 76.0 (CH_2); 75.9, 78.7, 79.3, 81.4, 87.5 (CH), 80.1 (C*q*), 128.1, 128.3, 128.4, 128.5, 128.8 (Ph); 138.2, 138.4, 138.8 (C*ipso*); 156.0, 204.2 (CO).

Anal. Calcd for $C_{42}H_{49}NO_8$: C, 72.50; H, 7.10; N, 2.01. Found: C, 72.36; H, 7.21; N, 2.12.

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