Three-Component Staudinger-Type Stereoselective Synthesis of *C*-Glycosyl-β-lactams and their Use as Precursors for *C*-Glycosyl Isoserines and Dipeptides. A Polymer-Assisted Solution-Phase Approach

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Dedicated to Professor J. Mulzer on the occasion of his 60th birthday.

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Abstract: A collection of 4-(*C*-galactosyl)- and 4-(*C*-ribosyl)-β-lactams featuring different substituents at C-3 and N-1 was prepared by combining in a one-pot procedure a formyl *C*-glycoside, a primary amine, and a substituted acetyl chloride in the presence of base (Staudinger-type reaction). Sulfonyl chloride and aminomethylated resins were used in sequence to remove excess of components and by-products. Two pure *C*-glycosyl-β-lactams were effectively transformed into *C*-glycosyl-*N*-Boc-β-amino-α-hydroxy esters (*C*-glycosyl isoserines) and a *C*-ribosyl dipeptide *via* base-promoted heterocycle ring opening by methanol and L-phenylalanine methyl ester, respectively.

Keywords: [2+2] cycloaddition; *C*-glycosides; *C*-glycosyl amino acids; β-lactams; multicomponent reaction

Introduction

In the course of our study on stereoselective multicomponent reactions (SMCRs) as a tool for the rapid construction of chiral heterocycle *C*-glycoconjugate systems with improved or new biological properties,[1] we became interested in the synthesis of 4-(*C*-glycosyl)-2-azetidinones **IV**, i.e., anomerically coupled sugar/β-lactam constructs (Figure 1). It is worth mentioning that the β-lactam skeleton is the key structural motif of several classes of antibiotics[2,3] such as penicillins, cephalosporins, thienamycins, and various monobactams, whose potency as inhibitors of different bacteria including the widely diffused *Staphylococcus aureus*, has been conveniently exploited for more than sixty years. Unfortunately, the longstanding use and abuse of these antibiotics have lead to the emergence of bacterial strain resistance to these drugs so that the design and synthesis of new families of β-lactam-containing molecules are being actively pursued. There is also a renewed interest in β-lactam derivatives, especially synthetic products, as non-antibiotic agents since compounds of this type have been shown to be inhibitors of prostate-specific antigen, human cytomegalovirus protease, thrombin, human leukocyte elastase, cholesterol absorption, and β-lactamase.[4] Another aspect underlying the importance of β-lactams in the strictly related domains of organic synthesis and medicinal chemistry is their application to the synthesis of other classes of biologically active compounds, especially densely functionalized β-amino acids, *via* the so-called β-lactam synthon methodology (β-LSM).[5] Hence, we were spurred to develop a chemically effective and operatively simple entry to the hitherto unreported class[6] of β-lactam *C*-glycoconjugates **IV** bearing the substituents R, R′, and the sugar moiety as elements of diversity, with the hope that these compounds would display new biological properties and serve as precursors for *C*-glycosyl-β-amino acids and/or unnatural glycopeptides.

Results and Discussion

Since the Staudinger [2+2] imine-ketene cycloaddition is by far the most versatile and simplest entry to the β-lactam system,[7] we envisaged the synthesis of **IV** by

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combining reagents which could generate *in situ* the above cycloaddition partners, thus giving rise to a one-pot, multicomponent reaction system. To this aim, the starting materials were easily identified as the commercially available substituted acetyl chlorides **III** and primary amines **II** as well as the readily available anomeric sugar aldehydes (formyl *C*-glycosides, **I**).[8]

According to the above synthetic plan, a chiral *C*-glycosylimine was generated in CH_2Cl_2 by mixing the β-*C*-galactosyl formaldehyde[8] **1** with an excess (1.5 equivs.) of *p*-methoxybenzylamine (R^1 = PMB) (Scheme 1). These unusual reaction conditions[9] ensured the complete consumption of the most costly reagent **1**. The unreacted alkylamine was easily removed from the solution by treatment with resin-supported sulfonyl chloride. The resulting heterogeneous mixture was then treated with (acetoxy)acetyl chloride (R^2 = Ac) (3.5 equivs.) and triethylamine (6 equivs.) to produce the corresponding acetoxy ketene.[10] After a suitable period of time (see Experimental Section) the reaction mixture was treated with nucleophilic aminomethylated resin which served to remove the excess of ketene and its unreacted precursor acetyl chloride, as well as the acid arising from decomposition of the latter. Furthermore, the same resin allowed the sequestering of aldehyde **1** which resulted from the partial hydrolysis of the *C*-galactosyl imine. Simple work-up (filtration and washing with water) of the resulting suspension and solvent evaporation afforded a mixture of 4-(*C*-galactosyl)-β-lactams (3*R*,4*S*)-**3a** and (3*S*,4*R*)-**3a** (for yield and ratio, see Table 1), slightly contaminated by the carboxylic acid amide [$AcOCH_2$ C(O)NHPMB]. The major stereoisomer (3*R*,4*S*)-**3a** shown in Scheme 1 was isolated in the pure state by chromatography.

While the conservation of the β-linkage at the anomeric carbon of the sugar moiety and the *cis*-relationship of the C3 and C4 protons of the β-lactam ring were easily established by ^{1}H NMR analysis, the absolute configuration of the latter carbon atom was assigned by chemical correlation of (3*R*,4*S*)-**3a** with a known compound. Thus, following the same reaction sequence described by Palomo and co-workers,[6] removal of the *O*-acetyl group from (3*R*,4*S*)-**3a** afforded **5** in almost quantitative

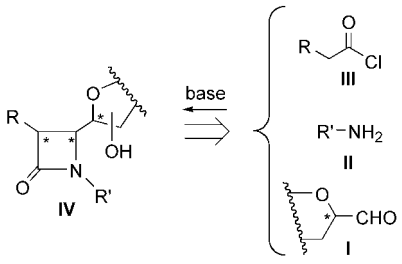
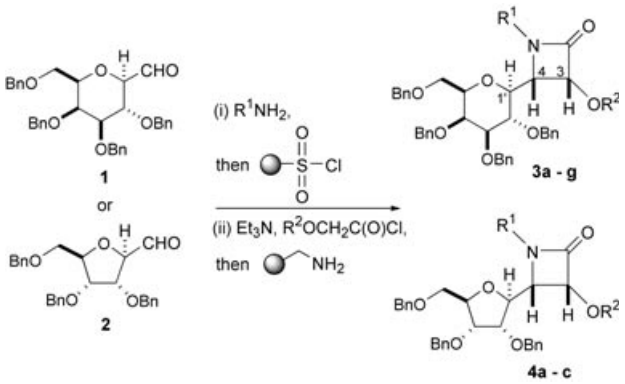


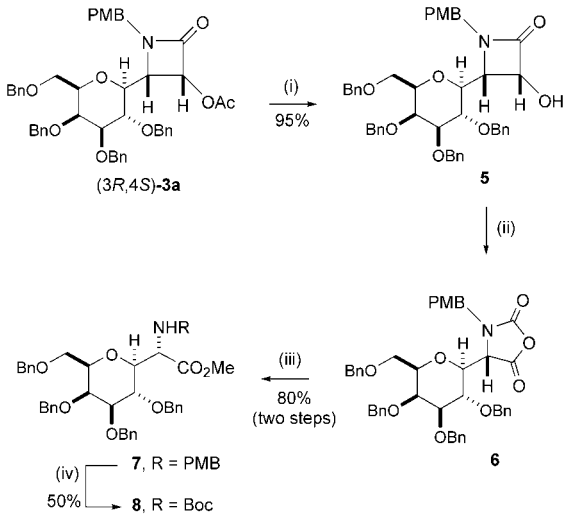
Figure 1. Reagents **I – III** for a multicomponent synthesis of *C*-glycosyl-β-lactams **IV**.



Scheme 1. *Reagents and conditions*: (i) R^1NH_2 (1.5 equivs.), 4 Å MS, CH_2Cl_2, 0 °C, 1 h, then polymer-bound sulfonyl chloride, 0 °C, 45 min; (ii) Et_3N (6.0 equivs.), (α-oxy)acetyl chloride (3.5 equivs.), CH_2Cl_2, −50 °C to r.t., 12 h, then aminomethylated polystyrene, r.t., 4 h.

yield (Scheme 2). Subsequent oxidative β-lactam ring enlargement to the α-amino acid *N*-carboxy anhydride (NCA) **6**, followed by ring opening by methanol, and final switching of the nitrogen protective group yielded the α-amino ester **8**. This compound was proved to be identical in all respects (NMR spectra and optical rotation value) to known (2*S*)-*N*-Boc-*C*-galactosylglycine methyl ester previously synthesized in our laboratory.[11]

Next, following the above optimized cyclocondensation protocol, also the *C*-ribosyl formaldehyde[8] **2** was effectively transformed (see Table 1) into the corresponding 4-(*C*-ribosyl)-β-lactam (3*R*,4*S*)-**4a** (Scheme 1).



Scheme 2. *Reagents and conditions*: (i) LiOH (2.0 equivs.), 30% H_2O_2 (6.0 equivs.), THF-H_2O (3:1), 0 °C, 2 h; (ii) TEMPO (1.0 equiv.), NaOCl, KBr, buffer phosphate solution, CH_2Cl_2, 0 °C, 15 min; (iii) MeOH, 50 °C, 8 h; (iv) Boc_2O (2.0 equivs.), dioxane, r.t. 24 h; then CAN (3.0 equivs.), MeCN-H_2O (4:1), r.t., 2 h.

The structure of this product was established by X-ray crystallography of the C3-OH-free derivative (see Supporting Information).[12] Other reactions were carried out using the above anomeric sugar aldehydes **1** and **2** and various pairs of primary amine and (alkoxy)acetyl chloride. In this way a small collection of ten 4-(*C*-glycosyl)-β-lactams **3a – g** and **4a – c** was prepared in satisfactory yields and selectivities (Table 1). Suitable protective groups were introduced at N1 and C3 of the β-lactam ring in view of the elaboration of these compounds toward fully deprotected systems for biological assays[13] and open-chain products *via* the β-LSM.[5] It is worth pointing out that the use of polymer-bound reagents is central to the effectiveness of this solution-phase chemistry. Their important function consists in removing the excess of reactants employed to draw key-steps to completion, thus allowing a one-pot, two-step, three-component reaction to be carried out efficiently and enabling the facile isolation of the final product(s) in an almost pure state.

Within the concept of β-LSM,[5] the ring opening of 3-alkoxy-β-lactams to give β-amino-α-hydroxy esters (isoserines) has been amply demonstrated.[5b] Accordingly, 4-(*C*-glycosyl)-β-lactams were envisaged as precursors for a new family of *C*-glycosylamino acids, i.e., *C*-glycosyl isoserines, and artificial glycopeptides. Examples of these transformations were carried out starting from appropriate *N*- and *O*-protected galactosyl and ribosyl derivatives (3*R*,4*S*)-**3e** and (3*R*,4*S*)-**4b** (Scheme 3). Very mild conditions were required in the basic alcoholysis of these β-lactams in order to avoid considerable loss of the configurational integrity of C3 as well as of the corresponding carbon atom in the resulting esters. Hence, taking advantage of the extensive experience of Palomo and co-workers in this chemistry,[14] the *N*-PMP group of (3*R*,4*S*)-**3e** was replaced by *N*-Boc and the resulting product **9** was subjected to Et_3N and DMAP-promoted methanolysis at room temperature.

Table 1. 4-*C*-Glycosylated β-lactams prepared by one-pot, two-step Staudinger reaction.

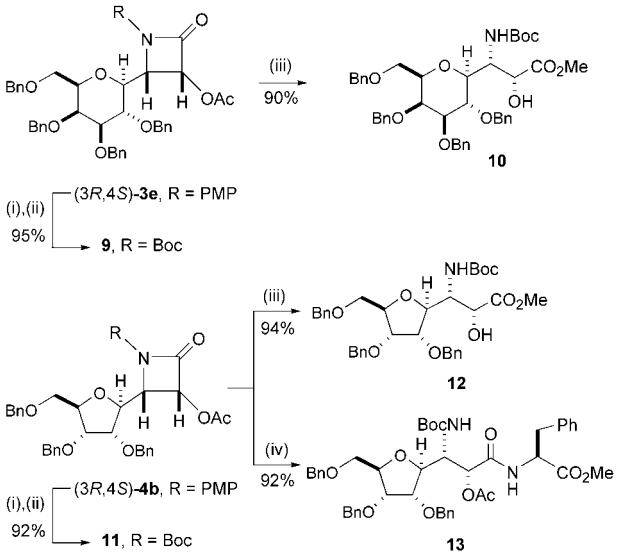
Entry		R^1	R^2	Yield [%][a]	de [%][b]
1	**3a**	PMB	Ac	94	70
2	**3b**	PMB	Bn	90	60
3	**3c**	Bn	Ac	92	70
4	**3d**	Bn	Bn	88	70
5	**3e**	PMP	Ac	68	50
6	**3f**	PMP	Bn	65	20
7	**3g**	PMB	Me	75	50
8	**4a**	PMB	Ac	92	90
9	**4b**	PMP	Ac	70	88
10	**4c**	PMP	Bn	68	75

[a] Overall yield of the mixture of diastereoisomers.
[b] Diastereomeric excess determined by ^1H NMR analysis of the crude reaction mixture

This reaction afforded the *C*-galactosyl isoserine methyl ester **10** in excellent isolated yield. No evidence of the presence of the C2 epimer was provided by NMR analysis of the crude reaction mixture. In the same way compound (3*R*,4*S*)-**4b** was transformed into the corresponding ester **12** in high yield and without the formation of the C2 epimer. In the same vein, another important transformation of (3*R*,4*S*)-**4b** was demonstrated to occur efficiently. In fact, β-lactams are known to be direct precursors for dipeptides containing β-amino-α-hydroxy acid fragments upon coupling with α-amino esters.[15] Accordingly, treatment of the *N*-Boc protected derivative **11** with L-phenylalanine methyl ester in the presence of DMAP afforded the *C*-ribosyl dipeptide **13** in excellent yield.

Conclusion

This explorative work on the potential of 4-(*C*-glycosyl)-β-lactams as precursors for unnatural *C*-glycosylamino acids and small peptides needs further research. In our laboratory this is being intensely pursued by addressing different modifications of the β-lactam ring and improved reaction conditions towards a fully automatized procedure suitable for parallel syntheses. The glycoconjugate library generation by combinatorial strategies [16] is, in fact, one of the topics of major interest in modern carbohydrate chemistry in the service of glycobiology.



Scheme 3. *Reagents and conditions*: (i) CAN (4.5 equivs.), MeCN-H_2O (4:1), −10 °C, 2 h; (ii) Boc_2O (1.5 equivs.), Et_3N (3.0 equivs.), DMAP (cat.), CH_2Cl_2 , r.t., 12 h; (iii) Et_3N (5.0 equivs.), DMAP (3.0 equivs.), MeOH, r.t., 48 h; (iv) H-Phe-OMe.HCl (2.0 equivs.), Et_3N (4.5 equivs.), DMAP (0.5 equivs.), CH_2Cl_2, r.t., 48 h.

Experimental Section

General Remarks

All moisture-sensitive reactions were performed under a nitrogen atmosphere using oven-dried glassware. Solvents were dried over standard drying agents and freshly distilled prior to use. Commercially available powdered 4 Å molecular sieves (5 μm average particle size) were used without further activation. Reactions were monitored by TLC on silica gel 60 F_{254} with detection by charring with sulfuric acid. Flash column chromatography was performed on silica gel 60 (230–400 mesh). Optical rotations were measured at 20 ± 2 °C in the stated solvent. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded for $CDCl_3$ solutions at room temperature unless otherwise specified. Assignments were aided by homo- and heteronuclear two-dimensional experiments. MALDI-TOF mass spectra were acquired using α-cyano-4-hydroxycinnamic acid as the matrix.

General procedures for all synthetic steps are described here while characterization data are reported only for representative *ribo* derivatives. Aldehydes **1** and **2** were prepared as described.[8] The *C*-galactosylglycine **8** is a known compound.[11]

General Procedure for Staudinger Reactions

A mixture of aldehyde **1** or **2** (0.50 mmol), activated 4 Å powdered molecular sieves (200 mg), and anhydrous CH_2Cl_2 (5 mL) was stirred at room temperature for 15 min and then cooled to 0 °C. To the mixture was slowly added the primary amine (0.75 mmol) and the suspension was stirred for an additional 1 h. Then polymer-bound sulfonyl chloride (500 mg, 1.00 mmol of a 2.0 mmol g^{-1} resin) was added in one portion and the mixture stirred at 0 °C for 45 min. The mixture was then cooled to −50 °C and Et_3N (418 μL, 3.00 mmol) and the (α-oxy)acetyl chloride (1.75 mmol) were added in this sequence. The resulting mixture was stirred overnight at room temperature and then aminomethylated polystyrene (555 mg, 1.50 mmol of a 2.7 mmol g^{-1} resin) was added in one portion. The suspension was stirred for additional 4 h then molecular sieves and resins were filtered off through a pad of Celite and washed thoroughly with CH_2Cl_2. The combined filtrates were washed with water (3×15 mL), dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with the suitable elution system to give the corresponding 4-*C*-glycosyl-β-lactam.

(3*R*,4*S*)-3-Acetoxy-4-(2′,3′,5′-tri-*O*-benzyl-β-D-ribofuranosyl)-1-(4-methoxyphenyl)-azetidin-2-one [(3*R*,4*S*)-4b]

Column chromatography with 5:2 cyclohexane-AcOEt afforded first (3*R*,4*S*)-**4b**; yield: 212 mg (67%) as a yellow syrup; $[\alpha]_D$: 5.5 (*c* 0.9, $CHCl_3$); ^{1}H NMR: δ = 7.40–7.20 and 6.80–6.60 (2 m, 19H, Ph), 6.02 (d, 1H, $J_{3,4}$ = 5.0 Hz, H-3), 4.57 and 4.53 (2d, 2H, J = 12.0 Hz, PhCH_2), 4.56 and 4.29 (2d, 2H, J = 11.5 Hz, PhCH_2), 4.46 (s, 2H, PhCH_2), 4.44 (dd, 1H, $J_{4,1'}$ = 6.0 Hz, H-4), 4.35 (dd, 1H, $J_{1',2'}$ = 6.2 Hz, H-1′), 4.20 (ddd, 1H, $J_{3',4'}$ = 5.0 Hz, $J_{4',5'a}$ = 3.5 Hz, $J_{4',5'b}$ = 4.5 Hz, H-4′), 3.96 (dd, 1H, $J_{2',3'}$ = 5.5 Hz, H-3′), 3.88 (dd, 1H, H-2′), 3.74 (s, 3H, OCH_3), 3.43 (dd, 1H, $J_{5'a,5'b}$ = 10.0 Hz, H-5′a), 3.37 (dd, 1H, H-5′b), 1.90 (s, 3H, CH_3); ^{13}C NMR: δ = 170.0, 162.2, 156.1, 137.7, 137.8, 138.0, 131.0, 129.0–127.0 (m, 15 C), 120.0, 111.9, 81.7, 80.0, 78.8, 77.2, 73.7, 73.0, 72.1, 71.9, 69.8, 59.0, 55.8, 20.3; MALDI-TOF MS: *m/z* = 638.7 (M^+ + H), 660.5 (M^+ + Na); anal. calcd. for $C_{38}H_{39}NO_8$ (637.72): C 71.57, H 6.16, N 2.20; found: C 71.60, H 6.18, N 2.25.

Eluted second was (3*S*,4*R*)-**4b** (10 mg, 3%) slightly contaminated by (3*R*,4*S*)-**4b**.

Conversion of the 4-(*C*-Galactosyl)-β-lactam (3*R*,4*S*)-3a into the (2*S*)-*N*-Boc-*C*-galactosylglycine Methyl Ester 8

(3*R*,4*R*)-4-(2′,3′,4′,6′-Tetra-*O*-benzyl-β-D-galactopyranosyl)-3-hydroxy-1-(4-methoxybenzyl)-azetidin-2-one (5): To a cooled (0 °C), stirred solution of (3*R*,4*S*)-**3a** (386 mg, 0.50 mmol) in THF (3 mL) and H_2O (1 mL) were added LiOH (24 mg, 1.00 mmol), and a 30% solution of H_2O_2 (0.30 mL, 3.00 mmol). The resulting mixture was stirred at the same temperature for 2 h, and then diluted with a 1.5 M solution of $Na_2S_2O_3$ (5 mL). Most of the THF was removed under vacuum from the mixture, which was then diluted with CH_2Cl_2 (100 mL), and washed with saturated aqueous $NaHCO_3$ ($3 \times$ 5 mL). The organic layer was dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 2:1 cyclohexane-AcOEt to give **5** as a colorless syrup; yield: 346 mg (95%); $[\alpha]_D$: −53.3 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3 + D_2O$): δ = 7.40–7.10 and 6.90–6.80 (2 m, 24H, Ph), 4.95 and 4.58 (2d, 2H, J = 11.2 Hz, PhCH_2), 4.87 and 4.53 (2d, 2H, J = 11.0 Hz, PhCH_2), 4.73 and 4.61 (2d, 2H, J = 11.8 Hz, PhCH_2), 4.52 (d, 1H, $J_{3,4}$ = 5.0 Hz, H-3), 4.42 and 4.38 (2d, 2H, J = 12.0 Hz, PhCH_2), 4.30 and 4.22 (2d, 2H, J = 14.0 Hz, PhCH_2), 4.14 (dd, 1H, $J_{1',2'}$ = 9.0 Hz, $J_{2',3'}$ = 9.2 Hz, H-2′), 3.96 (dd, 1H, $J_{3',4'}$ = 2.5 Hz, $J_{4',5'}$ ~ 0.5 Hz, H-4′), 3.76 (s, 3H, OCH_3), 3.75 (dd, 1H, $J_{4,1'}$ = 1.5 Hz, H-4), 3.48 (dd, 1H, H-3′), 3.47 (dd, 1H, $J_{5',6'a}$ = 8.0 Hz, $J_{6'a,6'b}$ = 9.0 Hz, H-6′a), 3.40 (dd, 1H, $J_{5',6'b}$ = 5.0 Hz, H-6′b), 3.38 (dd, 1H, H-1′), 3.18 (ddd, 1H, H-5′); MALDI-TOF MS: *m/z* = 730.5 (M^+ + H), 752.8 (M^+ + Na); anal. calcd. for $C_{45}H_{47}NO_8$ (729.86): C 74.05, H 6.49, N 1.92; found: C 74.10, H 6.52, N 1.90.

Methyl 3,7-Anhydro-4,5,6,8-tetra-*O*-benzyl-2-((4-methoxybenzyl)amino)-2-deoxy-D-*threo*-L-*galacto*-octanoate (7): To a stirred solution of **5** (365 mg, 0.50 mmol) in CH_2Cl_2 (4 mL) were added 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO; 78 mg, 0.50 mmol), and a solution of KBr (6.0 mg, 0.05 mmol) in H_2O (0.1 mL). The solution was then cooled to 0 °C, and aqueous NaOCl (5 mL) buffered at pH 7 (by the addition of 1 M phosphate buffer) was added. The resulting mixture was stirred at the same temperature for an additional 15 min, then diluted with CH_2Cl_2 (100 mL), and washed with a 10% solution of HCl (10 mL containing 125 mg of KI), a 10% solution of $Na_2S_2O_3$ (5 mL), and H_2O (5 mL). The organic layer was dried (Na_2SO_4), and concentrated to give the α-amino acid *N*-carboxy anhydride **6** as a crude material; yield: 353 mg (~95%); selected ^{1}H NMR data: δ = 7.40–7.10 and 6.90–6.80 (2 m, 24H, Ph), 4.52 and 4.48 (2d, 2H, J = 12.0 Hz, PhCH_2), 4.30 (dd, 1H, $J_{1',2'}$ = 9.0 Hz, $J_{2',3'}$ = 9.2 Hz, H-2′), 4.03 (dd, 1H, $J_{3',4'}$ = 2.5 Hz, $J_{4',5'}$ ~ 0.5 Hz, H-4′), 3.80 (s, 3H, OCH_3), 3.70 (dd, 1H, H-3′).

A solution of the above crude anhydride **6** (353 mg, ~0.48 mmol) in MeOH (4 mL) was stirred at 50 °C for 8 h,

then cooled to room temperature, and concentrated. The residue was eluted from a column of silica gel with 2.5:1 toluene-*i*-Pr_2O to give **7** as a white foam; yield: 293 mg (80% from **5**); $[\alpha]_D$: 19.3 (*c* 0.7, $CHCl_3$); ^1H NMR (C_6D_6): δ = 7.40–7.00 and 6.80–6.70 (2 m, 24H, Ph), 5.03 and 4.84 (2d, 2H, *J* = 11.0 Hz, PhCH_2), 4.95 and 4.54 (2d, 2H, *J* = 11.5 Hz, PhCH_2), 4.52 (dd, 1H, $J_{3,4}$ = 9.0 Hz, $J_{4,5}$ = 9.2 Hz, H-4), 4.35 and 4.31 (2d, 2H, *J* = 11.2 Hz, PhCH_2), 4.28 and 4.24 (2d, 2H, *J* = 12.0 Hz, PhCH_2), 4.04 (dd, 1H, $J_{2,3}$ = 1.5 Hz, H-3), 3.96 (d, 1H, H-2), 3.94 and 3.86 (2d, 2H, *J* = 13.5 Hz, PhCH_2), 3.84 (dd, 1H, $J_{5,6}$ = 2.5 Hz, $J_{6,7}$ ~ 0.5 Hz, H-6), 3.65 (dd, 1H, $J_{7,8a}$ = 7.5 Hz, $J_{8a,8b}$ = 9.0 Hz, H-8a), 3.59 (dd, 1H, $J_{7,8b}$ = 5.5 Hz, H-8b), 3.51 (ddd, 1H, H-7), 3.28 (s, 3H, OCH_3), 3.26 (s, 3H, OCH_3); MALDI-TOF MS: *m/z* = 732.9 (M^+ + H), 754.9 (M^+ + Na), anal. calcd. for $C_{45}H_{49}NO_8$ (731.87): C 73.85, H 6.75, N 1.91; found: C 73.88, H 6.70, N 1.93.

Methyl 3,7-Anhydro-4,5,6,8-tetra-*O*-benzyl-2-[(*tert*-butoxycarbonyl)amino]-2-deoxy-D-*threo*-L-*galacto*-octanoate (8): To a stirred solution of **7** (73 mg, 0.10 mmol) in dioxane (2 mL) was added di-*tert*-butyl dicarbonate (Boc_2O) (44 mg, 0.20 mmol) in one portion. The solution was stirred at room temperature for 24 h, and then concentrated. The residue was suspended with CH_2Cl_2 (50 mL) and washed with a 10% solution of citric acid (2 × 5 mL). The organic layer was dried (Na_2SO_4), and concentrated to give a ~1:1 mixture of the starting amino ester **7** and its *N*-Boc derivative.

To a stirred solution of the above crude mixture in MeCN (2 mL) and H_2O (0.5 mL) was added ceric ammonium nitrate (CAN) (164 mg, 0.30 mmol) in one portion. The resulting mixture was vigorously stirred at room temperature for 2 h, and then neutralized with a few drops of Et_3N. Most of the MeCN was removed under vacuum from the mixture, which was then diluted with CH_2Cl_2 (50 mL) and washed with a 10% solution of $Na_2S_2O_3$ (5 mL), and brine (5 mL). The organic layer was dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 1.5:1 toluene-*i*-Pr_2O to give **8** as an oil; yield: 36 mg (50% from **7**); $[\alpha]_D$: −3.0 (*c* 1.2, $CHCl_3$); lit.[11] $[\alpha]_D$: −2.6 (*c* 1.2, $CHCl_3$).

General Procedure for the Preparation of 3-Acetoxy-1-*N*-Boc-β-lactams

To a cooled (−10 °C), stirred solution of *N*-PMP-β-lactam (0.50 mmol) in CH_3CN (20 mL) and H_2O (5 mL) was slowly added a solution of ceric ammonium nitrate (1.23 g, 2.25 mmol) in H_2O (18 ml). The solution was stirred at −10 °C for 2 h then was quenched with aqueous saturated Na_2SO_3 solution (15 mL). The aqueous layer was extracted with AcOEt (3 × 40 mL), and the combined organic layer was washed with Na_2SO_3 solution, dried (Na_2SO_4), and concentrated to give the corresponding *N*-H-β-lactam as crude material.

To a stirred solution of the above crude *N*-H-β-lactam (~0.50 mmol), di-*tert*-butyl dicarbonate (164 mg, 0.75 mmol), and DMAP (15 mg, 0.12 mmol) in CH_2Cl_2 (5.0 mL) was slowly added Et_3N (209 μL, 1.50 mmol) at room temperature. The mixture was stirred for 18 h at room temperature then quenched with aqueous saturated NH_4Cl solution (15 mL). The mixture was extracted with AcOEt (3 × 30 mL). The combined extracts were dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with the suitable elution system to give the corresponding 1-*N*-Boc-4-*C*-glycosyl-β-lactam.

(3*R*,4*S*)-3-Acetoxy-4-(2′,3′,5′-tri-*O*-benzyl-β-D-ribofuranosyl)-1-(*tert*-butoxycarbonyl)-azetidin-2-one (11): Column chromatography with 5:2 cyclohexane-AcOEt afforded **11** as a yellow syrup; yield: 291 mg (92%); $[\alpha]_D$: 3.5 (*c* 0.9, $CHCl_3$); ^1H NMR: δ = 7.50–7.20 (m, 15H, Ph), 5.92 (d, 1H, $J_{3,4}$ = 6.0 Hz, H-3), 4.62 and 5.57 (2d, 2H, *J* = 11.0 Hz, PhCH_2), 4.59 (s, 2H, PhCH_2), 4.55 (s, 2H, PhCH_2), 4.46 (dd, 1H, $J_{4,1'}$ = 2.0 Hz, H-4), 4.39 (dd, 1H, $J_{2',3'}$ = 5.0 Hz, $J_{1',2'}$ = 7.0 Hz, H-2′), 4.25 (ddd, 1H, $J_{3',4'}$ = 5.5 Hz, $J_{4',5'a}$ = 4.5 Hz, $J_{4',5'b}$ = 5.5 Hz, H-4′), 4.10 (dd, 1H, H-1′), 3.92 (dd, 1H, H-3′), 3.55 (dd, 1 H, $J_{5'a,5'b}$ = 10.5 Hz, H-5′a), 3.43 (dd, 1H, H-5′b), 2.10 (s, 3H, CH_3), 1.42 (s, 9H, *t*-Bu); MALDI-TOF MS: *m/z* = 632.5 (M^+ + H), 654.5 (M^+ + Na), 670.3 (M^+ + K); anal. calcd. for $C_{36}H_{41}NO_9$ (631.71): C 68.45, H 6.54, N 2.22; found: C 68.48, H 6.55, N 2.25.

General Procedure for the Synthesis of *C*-Glycosyl-*N*-Boc-β-amino-α-hydroxy Esters

To a stirred solution of 3-acetoxy-1-*N*-Boc-β-lactam (0.20 mmol) and DMAP (73 mg, 0.60 mmol) in CH_3OH (5 mL) was slowly added Et_3N (139 μL, 1.00 mmol) at room temperature. The mixture was stirred at room temperature for 48 h, then the solvent was removed under reduced pressure and aqueous saturated NH_4Cl solution (8 mL) was added. The reaction mixture was then extracted with CH_2Cl_2 (3 × 20 mL), and the combined extracts were dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with the suitable elution system to give the corresponding *C*-glycosyl-*N*-Boc-β-amino-α-hydroxy methyl ester.

(2*R*,3*R*)-3-(2′,3′,5′-Tri-*O*-benzyl-β-D-ribofuranosyl)-3-*tert*-butoxycarbonylamino-2-hydroxypropionic acid methyl ester (12): Column chromatography with 2:1 cyclohexane-AcOEt afforded **12** as a yellow foam; yield: 117 mg (94%); $[\alpha]_D$: −16.5 (*c* 0.4, $CHCl_3$); ^1H NMR: δ = 7.50–7.20 (m, 15H, Ph), 5.65 (d, 1H, $J_{3,NH}$ = 10.0 Hz, NH), 4.62 and 4.55 (2d, 2H, *J* = 10.5 Hz, PhCH_2), 4.58 and 4.44 (2d, 2H, *J* = 12.0 Hz, PhCH_2), 4.53 and 4.44 (2d, 2H, *J* = 11.5 Hz, PhCH_2), 4.40 (d, 1H, $J_{2,3}$ = 3.5 Hz, H-2), 4.35 (dd, 1H, $J_{1',2'}$ = 6.0 Hz, $J_{3,1'}$ = 3.0 Hz, H-1′), 4.27 (ddd, 1H, H-3), 4.17 (ddd, 1H, $J_{3',4'}$ = 5.0 Hz, $J_{4',5'a}$ = 3.5 Hz, $J_{4',5'b}$ = 3.0 Hz, H-4′), 3.95 (dd, 1H, $J_{2',3'}$ = 5.0 Hz, H-2′), 3.90 (dd, 1H, H-3′), 3.78 (s, 3H, OCH_3), 3.55 (dd, 1H, $J_{5'a,5'b}$ = 10.0 Hz, H-5′a), 3.41 (dd, 1H, H-5′b), 3.30 (bs, 1H, OH), 1.42 (s, 9H, *t*-Bu); MALDI-TOF MS: *m/z* = 622.5 (M^+ + H), 644.3 (M^+ + Na), 660.8 (M^+ + K); anal. calcd for $C_{35}H_{43}NO_9$ (621.72): C 67.62, H 6.97, N 2.25; found: C 67.65, H 6.98, N 2.20.

Procedure for the Synthesis of Dipeptide 13

(2*S*)-2-[(2′*R*,3′*S*)-2′-Acetoxy-3′-(2″,3″,5″-tri-*O*-benzyl-β-D-ribofuranosyl)-3′-*tert*-butoxycarbonylaminopropionylamino]-3-phenylpropionic acid methyl ester (13): To a stirred solution of **11** (126 mg, 0.20 mmol), DMAP (12 mg, 0.10 mmol), and L-phenylalanine methyl ester hydrochloride (86 mg, 0.40 mmol) in CH_2Cl_2 (5 mL) was slowly added Et_3N (125 μL, 0.90 mmol) at room temperature. The mixture was stirred at room temperature for 48 h, then the solvent was removed under reduced pressure and aqueous saturated NH_4Cl solution (8 mL) was added. The reaction mixture was then extracted with CH_2Cl_2 (3 × 20 mL), and the combined extracts were dried (Na_2SO_4),

concentrated, and eluted from a column of silica gel with 2:1 cyclohexane-AcOEt to give **13** as a yellow foam; yield: 128 mg (92%); $[\alpha]_D$: 17.7 (*c* 0.9, $CHCl_3$); ^1H NMR: $\delta = 7.50-7.20$ and 7.15–7.00 (2 m, 20H, Ph), 6.57 (d, 1H, $J_{2,NH} = 8.0$ Hz, NH), 5.74 (d, 1H, $J_{3',N'H} = 10.0$ Hz, N′H), 5.38 (d, 1H, $J_{2',3'} = 5.0$ Hz, H-2′), 4.90 (ddd, 1H, $J_{2,3} = 7.0$ Hz, $J_{2,3a} = 6.5$ Hz, $J_{2,3b} = 6.5$ Hz, H-2), 4.60 and 4.54 (2d, 2H, $J = 11.5$ Hz, PhCH_2), 4.54 and 4.45 (2d, 2H, $J = 12.0$ Hz, PhCH_2), 4.54 and 4.42 (2d, 2H, $J = 12.0$ Hz, PhCH_2), 4.36–4.28 (m, 2H, H-3′, H-1″), 4.08 (ddd, 1H, $J_{3'',4''} = 5.0$ Hz, $J_{4'',5''a} = 3.5$ Hz, $J_{4'',5''b} = 4.0$ Hz, H-4″), 3.88 (dd, 1H, $J_{2'',3''} = 5.5$ Hz, H-3″), 3.83 (dd, 1 H, $J_{1'',2''} = 5.5$ Hz, H-2″), 3.72 (s, 3H, OCH_3), 3.52 (dd, 1H, $J_{5''a,5''b} = 10.0$ Hz, H-5″a), 3.37 (dd, 1H, H-5″b), 3.14 (d, 1H, 2 H-3), 1.98 (s, 3H, CH_3), 1.42 (s, 9H, *t*-Bu); MALDI-TOF MS: *m/z* = 695.9 ($M^+ + H$), 717.8 ($M^+ + Na$), 733.9 ($M^+ + K$); anal. calcd. for $C_{41}H_{44}NO_9$ (694.79): C 70.88, H 6.38, N 2.02; found: C 70.90, H 6.41, N 2.05.

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References and Notes

[1] a) A. Dondoni, A. Massi, S. Sabbatini, V. Bertolasi, *J. Org. Chem.* **2002**, *67*, 6979–6994; b) A. Dondoni, A. Massi, E. Minghini, V. Bertolasi, *Helv. Chim. Acta* **2002**, *85*, 3331–3348; c) A. Dondoni, A. Massi, E. Minghini, S. Sabbatini, V. Bertolasi, *J. Org. Chem.* **2003**, *68*, 6172–6183; d) A. Dondoni, A. Massi, *Mol. Diversity* **2003**, *6*, 261–270; e) A. Dondoni, A. Massi, E. Minghini, V. Bertolasi, *Tetrahedron* **2004**, *60*, 2311–2326.

[2] For reviews, see: a) *The Organic Chemistry of β-Lactams*, (Ed.: G. I. Georg), VCH, New York, **1993**; b) M. Kidwai, P. Sapra, K. R. Bhushan, *Curr. Med. Chem.* **1999**, *6*, 195–215.

[3] For several articles devoted to β-lactam chemistry and synthesis, see the thematic issue of *Tetrahedron* **2000**, *56*, 5553–5742.

[4] M. Carina, L. Delpiccolo, M. A. Fraga, E. G. Mata, *J. Comb. Chem.* **2003**, *5*, 208–210, and references cited therein.

[5] a) I. Ojima, in: *The Organic Chemistry of β-Lactams*, (Ed.: G. I. Georg), VCH, New York, **1993**, pp. 197–255; b) I. Ojima, S. Lin, *J. Org. Chem.* **1998**, *63*, 224–225, and references cited therein.

[6] The stereoselective synthesis of non-anomeric sugar β-lactams *via* [2+2] cycloaddition of achiral ketenes to chiral imines derived from cyclic dialdoses was reported earlier by Palomo and co-workers: C. Palomo, M. Oiarbide, A. Esnal, A. Landa, J. I. Miranda, A. Linden, *J. Org. Chem.* **1998**, *63*, 5838–5846; and more recently by Indian researchers: M. Arun, S. N. Joshi, V. G. Puranik, B. M. Bhawal, A. R. A. S. Deshmukh, *Tetrahedron* **2003**, *59*, 2309–2316.

[7] For reviews, see: a) G. I. Georg, V. T. Ravikumar, in: *The Organic Chemistry of β-Lactams*, (G. I. Georg), VCH, New York, **1993**, pp. 295–368; b) C. Palomo, J. M. Aizpurua, I. Ganboa, M. Oiarbide, *Eur. J. Org. Chem.* **1999**, 3223–3235.

[8] a) A. Dondoni, M.-C Scherrmann, *J. Org. Chem.* **1994**, *59*, 6404–6412; b) A. Dondoni, *Pure Appl. Chem.* **2000**, *72*, 1577–1588; c) A. Dondoni, P. Formaglio, A. Marra, A. Massi, *Tetrahedron* **2001**, 57, 7719–7727.

[9] In general an excess of aldehyde is employed for the *in situ* generation of the imine. These conditions are used to avoid the presence of unreacted amine which subtracts part of the ketene.

[10] For a fully automatable procedure, the ketene generation was also carried out by using the highly basic (but quite expensive) BEMP resin (polymer-bound triaminophosphonamide imine) that removes the trialkylammonium salt by-products and therefore simplifies considerably the work-up procedure. Full details of this methodology will be reported in a forthcoming paper. For the earlier use of the BEMP resin for ketene generation, see: A. E. Taggi, A. M. Hafez, H. Wack, B. Young, D. Ferraris, T. Lectka, *J. Am. Chem. Soc.* **2002**, *124*, 6626–6635.

[11] A. Dondoni, F. Junquera, F. L. Merchan, P. Merino, M.-C. Scherrmann, T. Tejero, *J. Org. Chem.* **1997**, *62*, 5484–5496.

[12] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 235150. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax.: (internat.) +44 1223/336–033; e-mail: deposit@ccdc.cam.ac.uk]. For enquires contact V. B. at the indicated address or by e-mail.

[13] The ease of removal of all protective groups from the β-lactam ring and sugar residue by CAN oxidation and hydrogenolysis was demonstrated in compounds (3*R*,4*S*)-**3b** and (3*R*,4*S*)-**4c**.

[14] C. Palomo, J. M. Aizpurua, C. Cuevas, A. Mielgo, R. Galarza, *Tetrahedron Lett.* **1995**, *36*, 9027–9030.

[15] a) I. Ojima, C. M. Sun, Y. H. Park, *J. Org. Chem.* **1994**, *59*, 1249–1250; b) C. Palomo, J. M. Aizpurua, C. Cuevas, *J. Chem. Soc. Chem. Commun.* **1994**, 1957–1958.

[16] a) P. M. St. Hilaire, M. Meldal, *Angew. Chem. Int. Ed.* **2000**, *39*, 1162–1179; b) A. Barkley, P. Arya, *Chem. Eur. J.* **2001**, *7*, 555–563.

