DOI: 10.1002/ejoc.200800521

Indium-Promoted Acyloxyallylation Reaction of Azetidine-2,3-diones in Aqueous Media: A New Route to Densely Functionalized 3-Substituted 3-Hydroxy-β-lactams

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Dedicated to Professor Dr. Carmen Pardo on the occasion of her 65th birthday and retirement

Keywords: Addition reactions / Ketones / C–C coupling / Heterocycles / Indium / Synthetic methods

Densely functionalized 3-substituted 3-hydroxy-β-lactams have been obtained by acyloxyallylation reaction of azetidine-2,3-diones with 3-bromopropenyl acetate or benzoate in aqueous media promoted by indium under Barbier conditions. Two new stereocenters were formed; the stereochemistry at the new C-3 quaternary center was fully controlled by placing a bulky chiral substituent at C-4. However, poor diastereoselectivities were observed in the new allylic stereocenter formed (up to 58 % *de*).

Introduction

3-Substituted 3-hydroxy-β-lactams are important substrates both for studies of biological activity and as versatile building blocks for β-amino acid synthesis, so the development of practical methods for their preparation is of much interest. In addition, the 3-substituted 3-hydroxy-β-lactam moiety represents an efficient carboxylate mimic,[1] shows promising activity in acyl CoA-cholesterol acyltransferase inhibition assays,[2] and is present in several pharmacologically active monobactams such as sulfacezin and related products[3] and in enzyme inhibitors such as tabtoxin and its analogues.[4] In addition, these compounds with the correct absolute configurations serve as precursors to the corresponding α-hydroxy-β-amino acids (isoserins), which are key components of a large number of therapeutically important compounds. As an example, (2*R*,3*S*)-3-amino-2-hydroxy-5-methylhexanoic acid (norstatine) and (3*R*,4*S*)-4-amino-3-hydroxy-5-methylheptanoic acid (statine) are residues for peptide inhibitors of enzymes such as rennin[5] and HIV-1 protease.[6] Moreover, phenylisoserine analogues are used to synthesize new taxoids.[7] On the other hand, the development of new carbon–carbon bond-forming reactions is of particular interest in organic synthesis, especially in the context of creating quaternary chiral centers in a stereoselective reaction.[8] In this context, the α-hydroxyallylation reaction of carbonyl compounds has been described[9,10] as a synthetic tool for the preparation of carbohydrates and related bioactive compounds containing a polyhydroxylated chain in their structural framework.[11] Continuing with our work on the asymmetric synthesis of nitrogenated compounds of biological interest,[12] we wish to report the acyloxyallylation reactions of enantiopure azetidine-2,3-diones in aqueous media,[13] which results in the corresponding 3-functionalized 3-hydroxy-β-lactams.

Results and Discussion

The starting materials, azetidine-2,3-diones **1a**–**c**, were efficiently prepared in optically pure form from aromatic or aliphatic (*R*)-2,3-*O*-isopropylideneglyceraldehyde-derived imines by Staundinger reaction with acetoxyacetyl chloride in the presence of Et_3N, followed by sequential transesterification and Swern oxidation, as we have previously reported (Scheme 1).[14]

3-Bromopropenyl acetate and benzoate were prepared following the experimental procedures described by Lombardo et al.[15]

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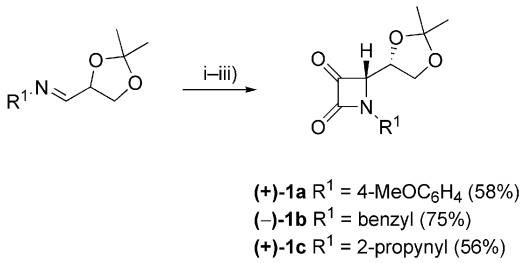
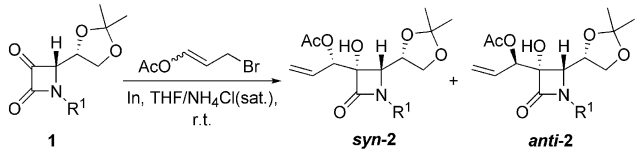


Scheme 1. Preparation of azetidine-2,3-diones **1**. Reagents and conditions: i) Et_3N, $AcOCH_2COCl$, CH_2Cl_2, room temp., overnight; ii) MeONa, MeOH, 0 °C to room temp., 30 min; iii) ClCOCOCl, DMSO, CH_2Cl_2, –78 °C, 1 h, then Et_3N, to room temp.

Having obtained the ketones, the next stage was set to carry out the key coupling reactions. As indium in aqueous solution has shown considerable promise in the addition of unsaturated halides to azetidine-2,3-diones **1**,[16] we decided to study the acyloxyallylation reaction with substrates **1**. We first investigated the reaction of azetidine-2,3-dione **1a** with 3-bromopropenyl acetate promoted by indium in aqueous media (in aqueous saturated THF/NH_4Cl; Table 1) using the same optimum conditions that we described previously for allylation and propagylation/allenylation reactions of the same substrates.[17] In the event, the corresponding addition product **2a** was obtained in a good yield (66%; Table 1, entry 1) with full control of the regiochemistry and total diastereoselectivity at the new quaternary stereocenter C-3, but with poor diastereoselectivity at the new allylic stereogenic center formed. Fortunately, both isomers were isolated after flash chromatography. In addition, it is important to note that the formation of byproducts associated with the transesterification processes were not observed.[18]

Table 1. Acetoxyallylation reactions of azetidine-2,3-diones **1** under aqueous conditions.



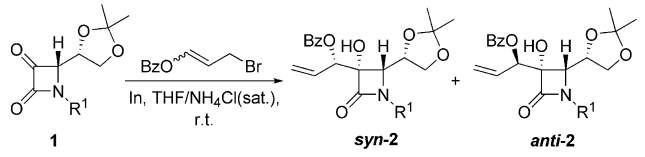
Entry	Ketone	R^1	Additive	*t* [h]	Product	*syn*/*anti*[a]	Yield[b] [%]
1	(+)-**1a**	PMP[c]	–	1	**2a**	55:45	66
2	(+)-**1a**	PMP	$InCl_3$	1	**2a**	55:45	48
3	(+)-**1a**	PMP	$HfCl_4$	1	**2a**	54:46	55
4	(–)-**1b**	Bn	–	1.2	**2b**	45:55	54
5	(+)-**1c**	2-Propynyl	–	1.2	**2c**	50:50	72

[a] The ratio was determined by integration of well-resolved signals in the ^1H NMR spectra of the crude reaction mixtures before purification. [b] Yield of the pure isolated product from appropriate analytical and spectroscopic data. [c] PMP = 4-$MeOC_6H_4$.

The acetoxyallylation reaction of ketones **1b** and **1c** provided inseparable mixtures of the corresponding *syn*/*anti* isomers of **2b** and **2c** (Table 1, entries 4 and 5). No better diastereoselectivity was observed when the reaction was carried out with a catalytic amount of the Lewis acid $InCl_3$ (Table 1, entry 2) or $HfCl_4$ (Table 1, entry 3).

To obtain better diastereoselectivity in the acyloxyallylation reaction, the next stage was to treat the azetidine-2,3-diones with 3-bromopropenyl benzoate (Table 2). We reasoned that by introducing a sterically more hindered group, the benzoyl group, the diastereoselectivity of the acyloxyallylation products could be improved. For this purpose, azetidine-2,3-dione **1a** was treated with 3-bromopropenyl benzoate (*E*/*Z* = 75:25) under the conditions described above, giving the corresponding addition product **2d** with better *syn*/*anti* diastereoselectivity (79:21) in 68% yield (Table 2, entry 1). Similar results were obtained when the reaction of **1a** was carried out with a catalytic amount of Lewis acid $InCl_3$ (Table 2, entry 2) or $HfCl_4$ (Table 2, entry 3), whereas with azetidine-2,3-diones **1b** and **1c** worse results in terms of selectivity were achieved (Table 2, entries 4 and 5). When the reaction was performed with (*E*)-3-bromopropenyl benzoate instead of the *E*/*Z* (75:25) mixture the same diastereoselectivities were obtained for compounds **2d**–**f**.

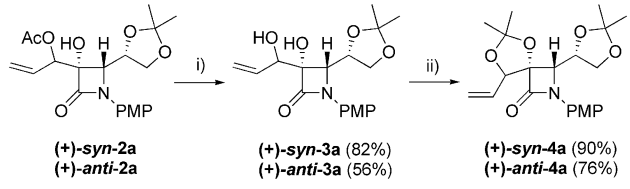
Table 2. Benzoyloxyallylation reactions of azetidine-2,3-diones **1** under aqueous conditions.



Entry	Ketone	R^1	Additive	*t* [h]	Product	*syn*/*anti*[a]	Yield[b] [%]
1	(+)-**1a**	PMP[c]	–	0.5	**2d**	79:21	68
2	(+)-**1a**	PMP	$InCl_3$	0.5	**2d**	78:22	66
3	(+)-**1a**	PMP	$HfCl_4$	1	**2d**	76:24	63
4	(–)-**1b**	Bn	–	1.2	**2e**	70:30	64
5	(+)-**1c**	2-Propynyl	–	1.2	**2f**	65:35	45

[a] The ratio was determined by integration of well-resolved signals in the ^1H NMR spectra of the crude reaction mixtures before purification. [b] Yield of the pure isolated product from appropriate analytical and spectroscopic data. [c] PMP = 4-$MeOC_6H_4$.

Configurational assignment for adducts *syn*- and *anti*-**2a** was achieved by derivatization to the corresponding bis-acetonides **4a** (Scheme 2). Thus, treatment of enantiomerically pure *syn*- and *anti*-**2a** in the presence of sodium methoxide at room temperature gave diols *syn*- and *anti*-**3a** in good yields, respectively. The reactions of compounds **3** with 2,2-dimethoxypropane and catalytic amounts of pyr-



Scheme 2. Synthesis of bis-acetonides **4**. Reagents and conditions: i) MeONa, MeOH, 0 °C to room temp., 30 min; ii) 2,2-dimethoxypropane, PPTS, Δ.

idinium *p*-toluensulfonate at reflux temperature provided the expected bis-acetonides *syn*- and *anti*-**4a** in excellent yields (90 and 76% respectively).

The structures (by DEPT, HETCOR, and COSY) and stereochemistries (by vicinal proton couplings and NOESY experiments) of compounds **2a**, **3a**, and **4a** were established by mono- and two-dimensional NMR techniques. The stereochemistries of the new allylic stereogenic center were deduced by comparison with NOE results for the isomers *syn*- and *anti*-**4a** (Figure 1). NOE irradiation of 4-H in *syn*-**4a** resulted in enhancement of the signal corresponding to 3′-H (4%). Conversely, the same NOE enhancement was observed for 4-H upon irradiation of 3′-H, which is consistent with a *syn* relative stereochemistry between 4-H and 3′-H and an *S* configuration at C-3′. A NOE enhancement of 0.4% for 4-H in *anti*-**4a** on irradiating the signal corresponding to 3′-H is in good agreement with an *anti* relative disposition between 3′-H and 4-H in *anti*-**4a** (*R* configuration at the stereogenic center C3′).

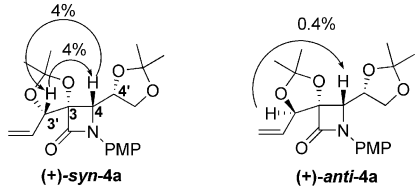


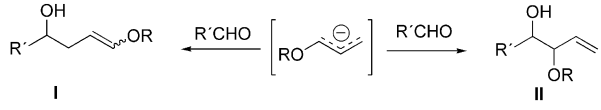
Figure 1. Selected NOE effects and configurations for adducts **4a**.

The transesterification reaction of the inseparable mixtures of acetates and benzoates *syn*/*anti*-**2b**–**f** under the above conditions provided the corresponding β-lactam diols **3** in good yields. The *syn* and *anti* isomers of compounds **3** were separated by flash chromatography (Table 3).

The absolute configurations of the new stereogenic centers in adducts **2b**–**f** and their corresponding diols **3** were determined by correlation of their spectroscopic pattern with those of **2a** and **3a** and by considering the results obtained in the NOE experiments on bis-acetonides *syn*- and *anti*-**4a**. Some spectroscopic correlations have been observed in the analysis of the ^{1}H and ^{13}C NMR spectra of the *syn* and *anti* compounds. For example, the signal corresponding to the olefinic proton H_2C=C*H* in the *syn* compounds **2**–**4** appears as a ddd in the range 5.87–6.11 ppm. However, for the *anti* compounds, this signal is shifted upfield by 0.08–0.20 ppm. The opposite effect was observed for the signal corresponding to the allylic proton 3′-H. This signal appears in the range 4.28–5.83 ppm for the *syn* isomers, whereas for the *anti* isomers, this signal is shifted downfield by 0.01–0.28 ppm.

Furthermore, it has been observed that the vicinal coupling constant between the allylic and vinylic protons of the *syn* isomers of **2** and **3** is 0.4–1.6 Hz smaller than for the *anti* isomers. The ^{13}C NMR spectroscopic data show some trends in the signals of the *syn* and *anti* isomers as well. As an example, for the *syn* compounds **2** and **3**, the signals corresponding to carbon C-4 resonate in the range 61.7–64.3 ppm, however, for the *anti* isomers, this signal is shifted upfield by 0.5–1.2 ppm. In contrast, the signals corresponding to C-3′ and the terminal olefinic carbon (=CH_2) in the *syn* isomers of **2** and **3** resonate upfield with respect to those of the *anti* isomers. However, we did not observe this pattern for the bis-acetonides **4**, probably due to conformational restrictions of the vinyl moiety.

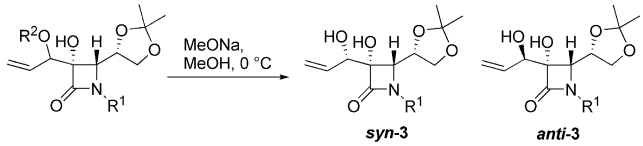
Nucleophilic addition of the organometallic reagent can occur from two different positions due to unsymmetrical substitution of the allylic reagent. A priori, two different products can be formed (types **I** and **II**, Scheme 3).[19] However, full regiochemical control in the reactions of our substrates **1** was observed. Compounds of type **II** were formed exclusively when the reactions were performed with indium as the metal promoter.



Scheme 3. Regiochemistry observed for the addition of 3-halopropenyl esters to aldehydes.

On the other hand, the stereoselectivity at the new stereogenic center C-3 is believed to be controlled by the bulky substituent at C-4; one face of the carbonyl group is blocked and thus the allylmetal species preferentially approaches the less hindered face (Figure 2). However, the *syn*/*anti* ratio observed at the allylic stereogenic center

Table 3. Preparation of diols **3**.



Entry	Compound (*syn*/*anti*)	R^1	R^2	*t* [h]	Products	Yield of *syn*-/*anti*-**3**[a] [%]
1	**2b** (45:55)	Bn	Ac	1	*syn*-**3b**/*anti*-**3b**	37/45
2	**2c** (50:50)	2-Propynyl	Ac	1	*syn*-**3c**/*anti*-**3c**	31/32
3	**2d** (79:21)	PMP[b]	Bz	5.5	*syn*-**3a**/*anti*-**3a**	62/17
4	**2e** (70:30)	Bn	Bz	8.5	*syn*-**3b**/*anti*-**3b**	66/28
5	**2f** (65:35)	2-Propynyl	Bz	7.5	*syn*-**3c**/*anti*-**3c**	24/14

[a] Yield of pure isolated isomers after chromatography from appropriate analytical and spectroscopic data. [b] PMP = 4-$MeOC_6H_4$.

formed in the acyloxyallylation reaction is governed by the steric size of the substituent attached to the organometallic reagent. Thus, better selectivities were obtained when the reaction was carried out with 3-bromopropenyl benzoate (R = Ph) than by using 3-bromopropenyl acetate (R = Ac).

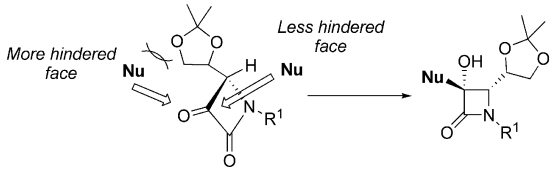


Figure 2. Model to explain the observed stereoselectivity for the acyloxyallylation reaction of azetidine-2,3-diones **1**.

Conclusions

A new protocol for the preparation of densely functionalized 3-substituted 3-hydroxy-β-lactams from enantiopure azetidine-2,3-diones and 3-bromopropenyl acetate or benzoate has been developed. The reaction proceeds in an aqueous environment under mild conditions promoted by indium.

Experimental Section

General Methods: Melting points were measured by using a Gallenkamp apparatus and are uncorrected. IR spectra were recorded with a Perkin–Elmer 781 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance-300, Varian VRX-300S or Bruker AC-200 spectrometer. NMR spectra were recorded in $CDCl_3$ solutions unless otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm) or $CDCl_3$ (^{13}C, 77.0 ppm). Mass spectra were recorded with a HP5989A spectrometer using the electronic impact (EI) method. Optical rotations were measured by using a Perkin–Elmer 241 polarimeter. Specific rotations $[a]_D$ are given in deg cm^2 g^{-1} at 25 °C and the concentration (c) is expressed in g per 100 mL. All commercially available compounds were used without further purification. Dichloromethane and triethylamine were distilled from CaH_2. Flame-dried glassware and standard Schlenk techniques were used for moisture-sensitive reactions. Flash chromatography was performed by using Merck silica gel 60 (230–400 mesh). Products were identified by TLC (Kieselgel 60F-254). UV light (λ = 254nm) and a solution of phosphomolybdic acid in EtOH (1 g of phosphomolybdic acid hydrate, 100 mL EtOH) were used to develop the plates.

General Procedure for the Acyloxyallylation of Azetidine-2,3-diones 1. Preparation of 3-Substituted 3-Hydroxy-β-lactams 2: 3-Bromopropenyl acetate or benzoate (2 mmol) was added to a well-stirred suspension of the α-keto lactam **1a**–**c** (1 mmol) and indium powder (2 mmol) in aq. saturated THF/NH_4Cl (1:5, 7.2 mL) at room temperature. After disappearance of the starting material (TLC), saturated aqueous sodium hydrogen carbonate (10 mL) was added at 0 °C and the mixture was warmed to room temperature before being extracted with ethyl acetate (4 × 15mL). The organic extract was washed with brine (30 mL), dried ($MgSO_4$), and concentrated under reduced pressure.

3-Hydroxyazetidin-2-one 2a: From azetidine-2,3-dione **1a** (99 mg, 0.34 mmol), 48 mg (36%) of *syn*-**2a** and 40 mg (30%) of *anti*-**2a** were isolated after purification by flash chromatography (hexanes/ethyl acetate, 10:1–7:1).

***syn*-2a:** Colorless oil. $[a]_D$ = +38.5 (c = 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.58 (AA′*XX*′, 2 H, C_6H_4), 6.85 (*AA*′XX′, 2 H, C_6H_4), 6.01 (ddd, ^3J = 17.3, 10.8, 5.4 Hz, 1 H, =CH-), 5.62 (d, ^3J = 5.4 Hz, 1 H, 3′-H), 5.43 (d, ^3J = 17.6 Hz, 1 H, =CH*H*), 5.42 (d, ^3J = 10.4 Hz, 1 H, =C*H*H), 4.80 (br. s, 1 H, OH), 4.44 (q, ^3J = 6.9 Hz, 1 H, 4'-H), 4.28 (dd, ^2J = 9.0, ^3J = 6.8 Hz, 1 H, OCH*H*), 4.12 (d, ^3J = 7.6 Hz, 1 H, 4-H), 3.81 (dd, ^2J = 9.1, ^3J = 6.6 Hz, 1 H, OC*H*H), 3.79 (s, 3 H, MeO), 2.05 (s, 3 H, MeCO), 1.49 and 1.35 (s, each 3 H, Me_2C) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 169.3 (COO), 165.8 (CON), 156.9 (C_{Ar} *ipso*-O), 130.8 (=CH-), 130.4 (C_{Ar} *ipso*-N), 120.1 (2 CH_{Ar}), 119.6 (=CH_2), 114.1 (2 CH_{Ar}), 109.8 (Me_2C), 84.6 (C-3), 76.5 (C-4′), 73.8 (C-3′), 66.8 (CH_2O), 64.3 (C-4), 55.4 (MeO), 26.6 and 25.1 (Me_2C), 20.8 (MeCO) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3332, 1751, 1729 cm^{-1}. MS (EI): *m*/*z* (%) = 391 (36) [M]$^+$, 149 (100). $C_{20}H_{25}NO_7$ (391.2): calcd. C 61.37, H 6.44, N 3.58; found C 61.69, H 6.65, N 3.42.

***anti*-2a:** Colorless oil. $[a]_D$ = +60.3 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.56 (AA′*XX*′, 2 H, C_6H_4), 6.87 (*AA*′XX′, 2 H, C_6H_4), 5.87 (ddd, ^3J = 17.0, 10.6, 6.4 Hz, 1 H, =CH-), 5.63 (d, ^3J = 6.4 Hz, 1 H, 3'-H), 5.49 (d, ^3J = 17.1 Hz, 1 H, =CH*H*), 5.37 (d, ^3J = 10.3 Hz, 1 H, =C*H*H), 4.43 (q, ^3J = 6.8 Hz, 1 H, 4'-H), 4.25 (dd, ^2J = 8.8, ^3J = 6.8 Hz, 1 H, OCH*H*), 4.09 (br. s, 1 H, OH), 4.09 (d, ^3J = 7.1 Hz, 1 H, 4-H), 3.80 (s, 3 H, MeO), 3.78 (dd, ^2J = 8.5, ^3J = 6.8 Hz, 1 H, OC*H*H), 2.14 (s, 3 H, MeCO), 1.49 and 1.35 (s, each 3 H, Me_2C) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 170.1 (COO), 165.5 (CON), 156.8 (C_{Ar} *ipso*-O), 130.3 (C_{Ar} *ipso*-N), 130.2 (=CH-), 120.8 (=CH_2), 120.1 (2 CH_{Ar}), 114.1 (2 CH_{Ar}), 109.8 (Me_2C), 84.7 (C-3), 76.6 (C-4′), 75.2 (C-3′), 66.7 (CH_2O), 63.3 (C-4), 55.4 (MeO), 26.5 and 25.0 (Me_2C), 20.9 (MeCO) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3356, 1748, 1730 cm^{-1}. MS (EI): *m*/*z* (%) = 391 (39) [M]$^+$, 149 (100). $C_{20}H_{25}NO_7$ (391.2): calcd. C 61.37, H 6.44, N 3.58; found C 61.59, H 6.22, N 3.73.

General Procedure for the Preparation of Diols 3a: Sodium methoxide (0.11 mmol) was added dropwise to a well-stirred solution of 3-substituted 3-hydroxy-β-lactam **2** (0.11 mmol) in methanol (1.05 mL) at 0 °C. After 50 min, a saturated aqueous sodium chloride solution was added (0.21 mL) and methanol was removed under reduced pressure. The mixture was extracted with ethyl acetate (4 × 5 mL), dried ($MgSO_4$), and concentrated under reduced pressure.

Diol *syn*-3a: From 3-substituted 3-hydroxy-β-lactam *syn*-**2a** (41 mg, 0.11 mmol), 30 mg (82%) of diol *syn*-**3a** was obtained as a white solid after purification by flash chromatography (hexanes/ethyl acetate, 3:1). M.p. 143–145 °C (hexanes/ethyl acetate). $[a]_D$ = +59.2 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.56 (AA′*XX*′, 2 H, C_6H_4), 6.87 (*AA*′XX′, 2 H, C_6H_4), 6.05 (ddd, ^3J = 17.2, 10.7, 5.3 Hz, =CH-), 5.52 (d, ^3J = 17.2 Hz, 1 H, =CH*H*), 5.38 (d, ^3J = 10.6 Hz, 1 H, =C*H*H), 4.43 (q, ^3J = 6.7 Hz, 1 H, 4'-H), 4.41 (d, ^3J = 5.3 Hz, 1 H, 3'-H), 4.24 (dd, ^2J = 8.9, ^3J = 6.8 Hz, 1 H, OCH*H*), 4.19 (d, ^3J = 6.7 Hz, 1 H, 4-H), 4.18 (br. s, 1 H, OH), 3.84 (dd, ^2J = 8.9, ^3J = 6.7 Hz, 1 H, OC*H*H), 3.79 (s, 3 H, MeO), 2.51 (br. s, 1 H, OH), 1.46 and 1.36 (s, each 3 H, Me_2C) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 167.1 (CON), 156.8 (C_{Ar} *ipso*-O), 134.6 (=CH-), 130.5 (C_{Ar} *ipso*-N), 120.2 (2 CH_{Ar}), 118.5 (=CH_2), 114.0 (2 CH_{Ar}), 109.8 (Me_2C), 85.6 (C-3), 76.6 (C-4′), 73.4 (C-3′), 66.8 (CH_2O), 63.8 (C-4), 55.4 (MeO), 26.5 and 25.1 (Me_2C) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3317, 1726 cm^{-1}. MS (EI): *m*/*z* (%)

= 349 (46) $[M]^+$, 149 (100). $C_{18}H_{23}NO_6$ (349.1): calcd. C 61.88, H 6.64, N 4.01; found C 61.59, H 6.72, N 3.98.

Diol *anti*-3a: From 3-substituted 3-hydroxy-β-lactam *anti*-**2a** (40 mg, 0.10 mmol), 20 mg (56%) of diol *anti*-**3a** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 3:1). $[a]_D$ = +74.3 (*c* = 1.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.52 (AA′*XX*′, 2 H, C_6H_4), 6.87 (*AA*′XX′, 2 H, C_6H_4), 5.90 (ddd, ^3J = 17.0, 10.8, 6.0 Hz, 1 H, =CH-), 5.54 (d, ^3J = 17.2 Hz, 1 H, =CH*H*), 5.35 (d, ^3J = 10.6 Hz, 1 H, =C*H*H), 4.50 (br. d, ^3J = 6.0 Hz, 1 H, 3'-H), 4.44 (q, ^3J = 6.6 Hz, 1 H, 4'-H), 4.22 (dd, ^2J = 8.9, ^3J = 6.8 Hz, 1 H, OCH*H*), 4.17 (d, ^3J = 6.4 Hz, 1 H, 4-H), 4.05 (br. s, 1 H, OH), 3.82 (dd, ^2J = 8.9, ^3J = 6.9 Hz, 1 H, OC*H*H), 3.80 (s, 3 H, MeO), 2.57 (br. s, 1 H, OH), 1.45 and 1.36 (s, each 3 H, Me_2C) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 167.2 (CON), 156.8 (C_{Ar} *ipso*-O), 133.6 (=CH-), 130.4 (C_{Ar} *ipso*-N), 120.1 (2 CH_{Ar}), 119.2 (=CH_2), 114.0 (2 CH_{Ar}), 109.8 (Me_2C), 85.4 (C-3), 76.7 (C-4′), 74.2 (C-3′), 66.8 (CH_2O), 63.2 (C-4), 55.4 (MeO), 26.5 and 25.1 (Me_2C) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3385, 1735 cm^{-1}. MS (EI): *m*/*z* (%) = 349 (45) $[M]^+$, 149 (100). $C_{18}H_{23}NO_6$ (349.1): calcd. C 61.88, H 6.64, N 4.01; found C 61.65, H 6.79, N 4.11.

General Procedure for the Preparation of β-Lactams 4: A solution of diol **3a** (45 mg, 0.13 mmol) and pyridinium *p*-toluensulfonate (0.03 mmol) in dimethoxypropane (4.5 mL) was heated at reflux temperature until complete disappearance of the starting material (TLC). The reaction mixture was cooled to room temperature and the solvent removed under reduced pressure. The crude product was purified by flash chromatography.

β-Lactam *syn*-4a: From diol *syn*-**3a** (20 mg, 0.06 mmol), 20 mg (90%) of compound *syn*-**4a** was obtained as a white solid after flash chromatography (hexanes/ethyl acetate, 3:1). M.p. 147–149 °C (hexanes/ethyl acetate). $[a]_D$ = +64.4 (*c* = 1.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.63 (AA′*XX*′, 2H, C_6H_4), 6.86 (*AA*′XX′, 2 H, C_6H_4), 5.93 (ddd, ^3J = 17.1, 10.1, 8.1 Hz, 1 H, =CH-), 5.49 (d, ^3J = 17.0 Hz, 1 H, =CH*H*), 5.33 (d, ^3J = 10.6 Hz, 1 H, =C*H*H), 4.61 (d, ^3J = 8.1 Hz, 1 H, 3'-H), 4.44 (dt, ^3J = 8.5, 6.7 Hz, 1 H, 4'-H), 4.33 (dd, ^2J = 8.6, ^3J = 7.0 Hz, 1 H, OCH*H*), 3.99 (d, ^3J = 8.6 Hz, 1 H, 4-H), 3.79 (s, 3 H, MeO), 3.76 (dd, ^2J = 8.6, ^3J = 6.3 Hz, 1 H, OC*H*H), 1.65 and 1.34 (s, each 3 H, Me_2C), 1.54 and 1.47 (s, each 3 H, Me_2C) ppm. ^{13}C NMR (75 MHz $CDCl_3$, 25 °C): δ = 164.7 (CON), 156.5 (C_{Ar} *ipso*-O), 131.1 (=CH-), 130.7 (C_{Ar} *ipso*-N), 122.0 (=CH_2), 119.6 (2 CH_{Ar}), 113.9 (2 CH_{Ar}), 112.1 (Me_2C), 109.8 (Me_2C), 90.5 (C-3), 81.7 (C-3′), 77.1 (C-4′), 66.6 (CH_2O), 63.2 (C-4), 55.4 (MeO), 27.7 and 24.7 (Me_2C), 26.6 and 26.1 (Me_2C) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1754 cm^{-1}. MS (EI): *m*/*z* (%) = 389 (89) $[M]^+$, 149 (100). $C_{21}H_{27}NO_6$ (389.2): calcd. C 64.77, H 6.99, N 3.60; found C 64.59, H 6.87, N 3.49.

β-Lactam *anti*-4a: From diol *anti*-**3a** (45 mg, 0.13 mmol), 38 mg (76%) of compound *anti*-**4a** was obtained as a white solid after flash chromatography (hexanes/ethyl acetate, 3:1). M.p. 98–100 °C (hexanes/ethyl acetate). $[a]_D$ = +36.8 (*c* = 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.65 (AA′*XX*′, 2 H, C_6H_4), 6.86 (*AA*′XX′, 2 H, C_6H_4), 5.86 (ddd, ^3J = 17.3, 10.3, 7.1 Hz, 1 H, =CH-), 5.43 (d, ^3J = 17.0 Hz, 1 H, =CH*H*), 5.39 (d, ^3J = 9.5 Hz, 1 H, =C*H*H), 4.89 (d, ^3J = 7.1 Hz, 1 H, 3'-H), 4.38 (dt, ^3J = 8.6, ^3J = 6.6 Hz, 1 H, 4'-H), 4.29 (dd, ^2J = 8.5, ^3J = 7.0 Hz, 1 H, OCH*H*), 4.19 (d, ^3J = 8.6 Hz, 1 H, 4-H), 3.79 (s, 3 H, MeO), 3.66 (dd, ^2J = 8.6, ^3J = 6.1 Hz, 1 H, OC*H*H), 1.58 and 1.33 (s, each 3 H, Me_2C), 1.55 and 1.53 (s, each 3 H, Me_2C) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 166.1 (CON), 156.5 (C_{Ar} *ipso*-O), 132.6 (=CH-), 130.8 (C_{Ar} *ipso*-N), 120.4 (=CH_2), 119.7 (2 CH_{Ar}), 113.9 (2 CH_{Ar}), 111.0 (Me_2C), 109.8 (Me_2C), 89.9 (C-3), 79.0 (C-3′), 77.0 (C-4′), 67.1 (CH_2O), 64.9 (C-4), 55.4 (MeO), 26.5 and 24.6 (s, each 3 H, Me_2C), 26.0 and 25.1 (s, each 3 H, Me_2C) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1752 cm^{-1}. MS (EI): *m*/*z* (%) = 389 (93) $[M]^+$, 149 (100). $C_{21}H_{27}NO_6$ (389.2): calcd. C 64.77, H 6.99, N 3.60; found C 64.69, H 7.01, N 3.72.

Supporting Information (see also the footnote on the first page of this article): Full spectroscopic and analytical data for previously unreported compounds not included in the Exp. Sect. are described in the Supporting Information. It contains compound characterization data and experimental procedures for compounds **2b**–**f** and **3b**,**c**, as well as ^1H and ^{13}C NMR chemical shifts of representative hydrogen and carbon atoms of compounds **2**, **3**, and **4**.

Acknowledgments

We would like to thank the Dirección General de Investigación, Ministerio de Educación y Ciencia (DGI-MEC) (Project CTQ2006-10292), the Comunidad Autónoma de Madrid (CCG-07-UCM/PPQ-2308) and the Universidad Complutense de Madrid (Grant GR74/07) for financial support. C. A. thanks the MEC for a Ramón y Cajal contract. G. C. and R. C. thank the MEC and UCM, respectively, for predoctoral grants.

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Received: May 29, 2008
Published Online: July 29, 2008

